

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

**(19) World Intellectual Property Organization
International Bureau**



A standard linear barcode is located at the bottom of the page, spanning most of the width. It is used for tracking and identification of the journal issue.

**(43) International Publication Date
25 July 2002 (25.07.2002)**

PCT

(10) International Publication Number
WO 02/057270 A1

(51) International Patent Classification⁷: C07D 491/04,
A61K 31/407, 31/4355, A61P 33/02

European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(21) International Application Number: PCT/GB02/00184

(22) International Filing Date: 17 January 2002 (17.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 0101179.0 17 January 2001 (17.01.2001) GB
60/275.359 13 March 2001 (13.03.2001) US

(71) **Applicant (for all designated States except US): INCENTA LIMITED [GB/GB]; St John's Innovation Centre, Cowley Road, Cambridge CB4 0WS (GB).**

(72) Inventor; and

(75) **Inventor/Applicant (for US only):** QUIBELL, Martin [GB/GB]; c/o Incenta Limited, Building 26, Chesterford Research Park, Little Chesterford, Cambridge CB10 1XL (GB).

(74) Agent: **SHEARD, Andrew, Gregory**; P.O. Box 521, Berkhamsted, Hertfordshire HP4 1YP (GB).

(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

Declarations under Rule 4.17:

— as to the identity of the inventor (Rule 4.17(i)) for the following designations **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)**

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG) of inventorship (Rule 4.17(iv)) for US only.

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF CRUZIPAIN AND OTHER CYSTEINE PROTEASES

$$\begin{array}{c}
 \text{U} - (\text{V})_m - (\text{W})_n - (\text{X})_o - \text{Y} - \text{N}^{\text{Q}} \left(\text{P}_1 \right) \text{C}_1 \text{Z} \text{C}_2 \text{O} \text{R}^1 \\
 | \\
 \text{C}_1 \text{C}_2
 \end{array} \quad (I)$$

$$\begin{array}{c}
 \text{U} \xrightarrow{(\text{V})_m} \text{W} \xrightarrow{(\text{X})_n} \text{Y} \xrightarrow{\text{Q}} \text{N}^{\text{P}_2} \text{C}^{\text{P}_1} \text{Z} \xrightarrow{\text{O}} \text{R}^1
 \end{array} \quad (\text{II})$$

(57) Abstract: Compounds of general formula (I) or general formula (II) wherein R¹, P₁, P₂, Q, Y, (X)_n, (W)_m, (V)_m, Z and U are as defined in the specification, are inhibitors of cruzipain and other cysteine protease inhibitors and are useful as therapeutic agents, for example in Chagas' disease, or for validating therapeutic target compounds.

INHIBITORS OF CRUZIPAIN AND OTHER CYSTEINE PROTEASES

THIS INVENTION relates to compounds which are inhibitors of the protease cruzipain, a gene product of the *Trypanosoma cruzi* parasite. In particular, the invention provides compounds that are useful for the therapeutic treatment of *Trypanosoma cruzi* infection, to the use of these compounds, and to pharmaceutical compositions comprising them. Furthermore, this invention relates to compounds which are inhibitors across a broad range of cysteine proteases, to the use of these compounds, and to pharmaceutical compositions comprising them. Such compounds are useful for the therapeutic treatment of diseases in which participation of a cysteine protease is implicated.

The trypanosomal family of parasites have a substantial worldwide impact on human and animal healthcare (McKerrow, J. H., *et al*, *Ann. Rev. Microbiol.* 47, 821-853, 1993). One parasite of this family, *Trypanosoma cruzi*, is the causative agent of Chagas' disease, which affects in excess of twenty million people annually in Latin and South America, is the leading cause of heart disease in these regions and results in more than 45,000 deaths per annum (Centers for Disease Control and prevention website). In addition, with the increase in migration of the infected population from rural to urban sites and movements from South and Central America into North America, the infection is spreading via blood transfusions, and at birth. The present treatments of choice for *Trypanosoma cruzi* infection, nifurtimox and benznidazole (an NADH fumarate reductase inhibitor, Turrens, JF, *et al*, *Mol Biochem Parasitol.*, 82(1),125-9, 1996) are at best moderately successful, achieving ~60% cure during the acute phase of infection (see Docampo, R. *Curr. Pharm. Design*, 7, 1157-1164, 2001 for a general discussion) whilst not being prescribed at all during the chronic phase where cardiomyopathy associated heart failure often occurs (Kirchhoff, L. V. *New Engl. J. Med.*, 329, 639-644, 1993). Additionally, these two drugs have serious adverse toxic effects, requiring close medical supervision during treatment, and have been shown to induce chromosomal damage in chagasic infants (Gorla, N. B. *et al*, *Mutat. Res.* 206, 217-220, 1988). Therefore, a strong medical need exists for new effective drugs for the chemotherapeutic treatment of *Trypanosoma cruzi* infection.

Classically, the identification of enzymes found to be crucial for the establishment or propagation of an infectious disease has been instrumental in the development of successful drugs such as antivirals (e.g. HIV aspartyl protease inhibitors) and anti-
5 bacteria (e.g. β -lactam antibiotics). The search for a similar Achilles heel in parasitic infections has examined numerous enzymes (e.g. parasitic dihydrofolate reductase, see Chowdhury, S. F. *et al*, *J. Med. Chem.*, 42(21), 4300-4312, 1999; trypanothione reductase, see Li, Z. *et al*, *Bioorg. Med. Chem. Lett.*, 11(2), 251-254, 2001; parasitic glyceraldehydes-3-phosphate dehydrogenase, see Aranov, A. M. *et*
10 *al*, *J. Med. Chem.*, 41(24), 4790-4799, 1998). A particularly promising area of research has identified the role of cysteine proteases, encoded by the parasite, that play a pivotal role during the life cycle of the parasite (McKerrow, J. H., *et al*, *Bioorg. Med. Chem.*, 7, 639-644, 1999). Proteases form a substantial group of biological molecules which to date constitute approximately 2% of all the gene
15 products identified following analysis of several genome sequencing programmes (e.g. see Southan, C. *J. Pept. Sci.*, 6, 453-458, 2000). Proteases have evolved to participate in an enormous range of biological processes, mediating their effect by cleavage of peptide amide bonds within the myriad of proteins found in nature. This hydrolytic action is performed by initially recognising, then binding to, particular
20 three-dimensional electronic surfaces displayed by a protein, which aligns the bond for cleavage precisely within the protease catalytic site. Catalytic hydrolysis then commences through nucleophilic attack of the amide bond to be cleaved either via an amino acid side-chain of the protease itself, or through the action of a water molecule that is bound to and activated by the protease. Proteases in which the attacking
25 nucleophile is the thiol side-chain of a Cys residue are known as cysteine proteases. The general classification of 'cysteine protease' contains many members found across a wide range of organisms from viruses, bacteria, protozoa, plants and fungi to mammals.

30 Biological investigation of *Trypanosoma cruzi* infection has highlighted a number of specific enzymes that are crucial for the progression of the parasite's life cycle. One such enzyme, cruzipain, a cathepsin L-like cysteine protease, is a clear therapeutic

target for the treatment of Chagas' disease ((a) Cazzulo, J. J. *et al*, *Curr. Pharm. Des.*, 7, 1143-1156, 2001; (b) Caffrey, C. R. *et al*, *Curr. Drug Targets*, 1, 155-162, 2000). Although the precise biological role of cruzipain within the parasite's life cycle remains unclear, elevated cruzipain messenger RNA levels in the epimastigote 5 developmental stage indicate a role in the nutritional degradation of host-molecules in lysosomal-like vesicles (Engel, J. C. *et al*, *J. Cell. Sci.*, 111, 597-606, 1998). The validation of cruzipain as a viable therapeutic target has been achieved with increasing levels of complexity. Addition of a general cysteine protease inhibitor, Z-Phe-Ala-FMK to *Trypanosoma cruzi*-infected mammalian cell cultures blocked 10 replication and differentiation of the parasite, thus arresting the parasite life cycle (Harth, G., *et al*, *Mol. Biochem. Parasitol.* 58, 17-24, 1993). Administration of a vinyl sulphone-based inhibitor in a *Trypanosoma cruzi*-infected murine animal model not only rescued the mice from lethal infections, but also produced a complete 15 recovery (Engel, J. C. *et al*, *J. Exp. Med.*, 188(4), 725-734, 1998). Numerous other *in vivo* studies have confirmed that infections with alternative parasites such as *Leishmania major* (Selzer, P. M. *et al*, *Proc. Nat'l. Acad. Sci. U.S.A.*, 96, 11015-11022, 1999), *Schistosoma mansoni* and *Plasmodium falciparum* (Olson, J. E. *et al*, *Bioorg. Med. Chem.*, 7, 633-638, 1999) can be halted or cured by treatment with cysteine protease inhibitors.

20

A variety of synthetic approaches have been described towards the design of cruzipain inhibitors. However, although providing a biological 'proof-of-principle' for the treatment of *Trypanosoma cruzi* infection, current inhibitors exhibit a number 25 of biochemical and physical properties that may preclude their clinical development. (e.g. see (a) Brinen, L. S. *et al*, *Structure*, 8, 831-840, 2000, peptidomimetic vinyl sulphones, possible adverse mammalian cell toxicity (see McKerrow, J. H. and Engel, J. unpublished results cited in Scheidt, K. A. *et al*, *Bioorg. Med. Chem.*, 6, 2477-2494, 1998); (b) Du, X. *et al*, *Chem. Biol.*, 7, 733-742, 2000, aryl ureas, generally with low μ M activity, and high ClogP values, thus poor aqueous solubility 30 and probably low oral bioavailability; (c) Roush, W. R. *et al*, *Tetrahedron*, 56, 9747-9762, 2000, peptidyl epoxysuccinates, irreversible inhibitors, with potent activity verses house-keeping mammalian proteases such as cathepsin B; (d) Li, R. *et al*,

Bioorg. Med. Chem. **4**(9), 1421-1427, 1996, bisarylacylhydrazides and chalcones, polyhydroxylated aromatics; (e) US6143931, WO 9846559, non-peptide α -ketoamides). Of the many different approaches to enzyme inhibition to date, only the cruzipain protease inhibitors have proven effective in curing disease-related animal 5 models of *Trypanosoma cruzi* infection. Therefore, a clear medical need exists to progress these 'proof-of-principle' findings towards clinical candidates, suitable for human use, through the discovery of more efficacious cruzipain inhibitors that have a desirable combination of potency, selectivity, low toxicity and optimised pharmacokinetic parameters.

10

Cruzipain and indeed many other crucial parasitic proteases belong to the papain-like CA C1 family and have close structural mammalian homologues. Cysteine proteases are classified into 'clans' based upon a similarity in the three-dimensional structure or a conserved arrangement of catalytic residues within the protease primary 15 sequence. Additionally, 'clans' are further classified into 'families' in which each protease shares a statistically significant relationship with other members when comparing the portions of amino acid sequence which constitute the parts responsible for the protease activity (see Barrett, A.J *et al*, in 'Handbook of Proteolytic Enzymes', Eds. Barrett, A. J., Rawlings, N. D., and Woessner, J. F. Publ. Academic 20 Press, 1998, for a thorough discussion). To date, cysteine proteases have been classified into five clans, CA, CB, CC, CD and CE (Barrett, A. J. *et al*, 1998). A protease from the tropical papaya fruit 'papain' forms the foundation of clan CA, which currently contains over 80 distinct and complete entries in various sequence databases, with many more expected from the current genome sequencing efforts. 25 Proteases of clan CA/family C1 have been implicated in a multitude of disease processes e.g. human proteases such as cathepsin K (osteoporosis), cathepsin S (autoimmune disorders), cathepsin L (metastases) or parasitic proteases such as falcipain (malaria parasite *Plasmodium falciparum*), cruzipain (*Trypanosoma cruzi* infection). Recently a bacterial protease, staphylopain (*S. aureus* infection) has also 30 been tentatively assigned to clan CA. X-ray crystallographic structures are available for a range of the above mentioned proteases in complex with a range of inhibitors e.g. papain (PDB entries, 1pad, 1pe6, 1pip, 1pop, 4pad, 5pad, 6pad, 1ppp, 1the, 1csb,

1huc), cathepsin K (1au0, 1au2, 1au3, 1au4, 1atk, 1mem, 1bgo, 1ayw, 1ayu), cathepsin L (1cs8), cathepsin S (currently on-hold, but published McGrath, M. E. *et al*, *Protein Science*, 7, 1294-1302, 1998), cruzain (a recombinant form of cruzipain see Eakin, A. E. *et al*, 268(9), 6115-6118, 1993) (1ewp, 1aim, 2aim, 1F29, 1F2A, 5 1F2B, 1F2C), staphylopain (1cv8). Each of the structures displays a similar overall active-site topology, as would be expected by their 'clan' and 'family' classification and such structural similarity exemplifies one aspect of the difficulties involved in discovering a selective inhibitor of cruzipain suitable for human use. However, subtle differences in terms of the depth and intricate shape of the active site groove of each 10 CA C1 protease are evident, which may be exploited for selective inhibitor design. Additionally, many of the current substrate-based inhibitor complexes of CA C1 family proteases show a series of conserved hydrogen bonds between the inhibitor and the protease backbone, which contribute significantly to inhibitor potency. Primarily a bidentate hydrogen-bond is observed between the protease Gly66 (C=O)/ 15 inhibitor N-H and the protease Gly66(NH)/inhibitor (C=O), where the inhibitor (C=O) and (NH) are provided by an amino acid residue NHCHRCO that constitutes the S2 sub-site binding element within the inhibitor (see Berger, A. and Schechter, I. *Philos. Trans. R. Soc. Lond. [Biol. J.*, 257, 249-264, 1970 for a description of protease binding site nomenclature). A further hydrogen-bond between the protease main- 20 chain (C=O) of asparagine or aspartic acid (158 to 163, residue number varies between proteases) and an inhibitor (N-H) is often observed, where the inhibitor (N-H) is provided by the S1 sub-site binding element within the inhibitor. Thus, the motif X-NHCHRCO-NH-Y is widely observed amongst the prior art substrate-based 25 inhibitors of CA C1 proteases.

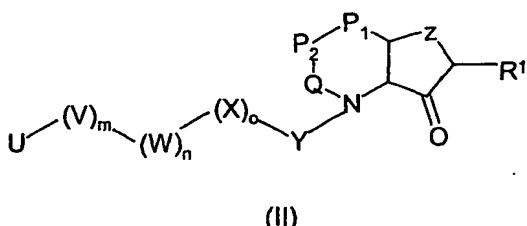
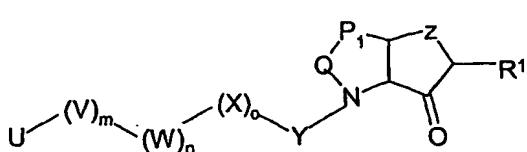
In the prior art, the development of cysteine protease inhibitors for human use has recently been an area of intense activity. Considering the CA C1 family members, particular emphasis has been placed upon the development of inhibitors of human cathepsins, primarily cathepsin K (osteoporosis), cathepsin S (autoimmune disorders) 30 and cathepsin L (metastases), through the use of peptide and peptidomimetic nitriles (e.g. see WO-A-0109910, WO-A-0051998, WO-A-0119816, WO-A-9924460, WO- A-0049008, WO-A-0048992, WO-A-0049007, WO-A-0130772, WO-A-0055125,

WO-A-0055126, WO-A-0119808, WO-A-0149288, WO-A-0147886), linear and cyclic peptide and peptidomimetic ketones (e.g. see Veber, D. F. and Thompson, S. K., *Curr. Opin. Drug Discovery Dev.*, 3(4), 362-369, 2000, WO-A-0170232, WO-A-0178734, WO-A-0009653, WO-A-0069855, WO-A-0029408, WO-A-0134153 to 5 WO-A-0134160, WO-A-0029408, WO-A-9964399, WO-A-9805336, WO-A-9850533), ketoheterocycles (e.g. see WO-A-0055144, WO-A-0055124) and monobactams (e.g. see WO-A-0059881, WO-A-9948911, WO-A-0109169). The prior art describes potent *in vitro* inhibitors, but also highlights the many difficulties in developing a human therapeutic. For example, WO-A-9850533 and WO-A-10 0029408 describe compounds that may be referred to as cyclic ketones and are inhibitors of cysteine proteases with a particular reference towards papain family proteases and as a most preferred embodiment, cathepsin K. WO-A-9850533 describes compounds subsequently detailed in the literature as potent inhibitors of cathepsin K with good oral bioavailability (Witherington, J., 'Tetrahydrofurans as 15 Selective Cathepsin K Inhibitors', RSC meeting, Burlington House, London, 1999). The compounds of WO-A-9850533 were reported to bind to cathepsin K through the formation of a reversible covalent bond between the tetrahydrofuran carbonyl and the active site catalytic cysteine residue (Witherington, J., 1999). Additionally, the same cyclic ketone compounds are described in WO-A-9953039 as part of a wide-ranging 20 description of inhibitors of cysteine proteases associated with parasitic diseases, with particular reference to the treatment of malaria by inhibition of falcipain. However, subsequent literature describes the cyclic ketone compounds of WO-A-9850533 to be unsuitable for further development or for full pharmacokinetic evaluation due to a physiochemical property of the inhibitors, the poor chiral stability of the α -aminoketone chiral centre (Marquis, R. W. *et al*, *J. Med. Chem.*, 44(5), 725-736, 25 2001). WO-A-0069855 describes compounds that may also be referred to as cyclic ketones with particular reference towards inhibition of cathepsin S. The compounds of WO-A-0069855 are considered to be an advance on compounds of WO-A-9850533 due to the presence of the β -substituent on the cyclic ketone ring system 30 that provides chiral stability to the α -carbon of the cyclic ketone ring system. However, the compounds of WO-A-0069855 and indeed those of WO-A-9850533 describe a requirement for the presence of the potential hydrogen-bonding motif X-

NHCHR_nCO-NH-Y that is widely observed amongst the prior art substrate-based inhibitors of CA C1 proteases.

It has now been discovered that certain compounds, defined by general formulae (I) and (II), are potent and selective cruzipain protease inhibitors which are useful in the treatment of *Trypanosoma cruzi* infection. Other compounds defined by general formulae (I) and (II) are protease inhibitors across a broad range of CA C1 cysteine proteases and compounds useful in the treatment of diseases caused by cysteine proteases. Compounds described by general formulae (I) and (II) do not contain the **X-NHCHR₁CO-NH-Y** motif that is widely observed amongst the prior art substrate-based inhibitors of CA C1 proteases, yet surprisingly compounds defined by general formulae (I) and (II) retain good potency. The present invention provides substituted tetrahydrofuro[3,2-*b*]pyrrol-3-one, tetrahydrothieno[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydrocyclopenta[*b*]pyrrol-6-one, tetrahydrofuro[3,2-*c*]pyrazol-6-one, tetrahydrothieno[3,2-*c*]pyrazol-6-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one, hexahydrocyclopentapyrazol-6-one, hexahydrofuro[3,2-*b*]pyridin-3-one, hexahydrothieno[3,2-*b*]pyridin-3-one, octahydropyrrolo[3,2-*b*]pyridin-3-one, octahydrocyclopenta[*b*]pyridin-7-one, hexahydrofuro[3,2-*c*]pyridazin-7-one, hexahydrothieno[3,2-*c*]pyridazin-7-one, octahydropyrrolo[3,2-*c*]pyridazin-7-one or octahydrocyclopenta[*c*]pyridazin-7-one bicyclic compounds defined by general formulae (I) and (II).

Accordingly, the first aspect of the invention provides a compound according to general formula (I) or general formula (II): -



25

(1)

(11)

wherein: R^1 = C_{0-7} -alkyl (when $C = 0$, R^1 is simply hydrogen), C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl (when $C = 0$, R^1 is simply an aromatic moiety Ar);

$Z = O, S, CR^2R^3$ or NR^4 , where R^4 is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl;

5 $P^1 = CR^5R^6$,

$P^2 = CR^7R^8$,

$Q = CR^9R^{10}$ or NR^{11} , where R^{11} is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl;

10 Each of $R^2, R^3, R^5, R^6, R^7, R^8, R^9$ and R^{10} is independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl, $O-C_{0-7}$ -alkyl, $O-C_{3-6}$ -cycloalkyl, $O-Ar-C_{0-7}$ -alkyl, $S-C_{0-7}$ -alkyl, $S-C_{3-6}$ -cycloalkyl, $S-Ar-C_{0-7}$ -alkyl, $NH-C_{0-7}$ -alkyl, $NH-C_{3-6}$ -cycloalkyl, $NH-Ar-C_{0-7}$ -alkyl, $N(C_{0-7}$ -alkyl)₂, $N(C_{3-6}$ -cycloalkyl)₂ or $N(Ar-C_{0-7}$ -alkyl)₂;

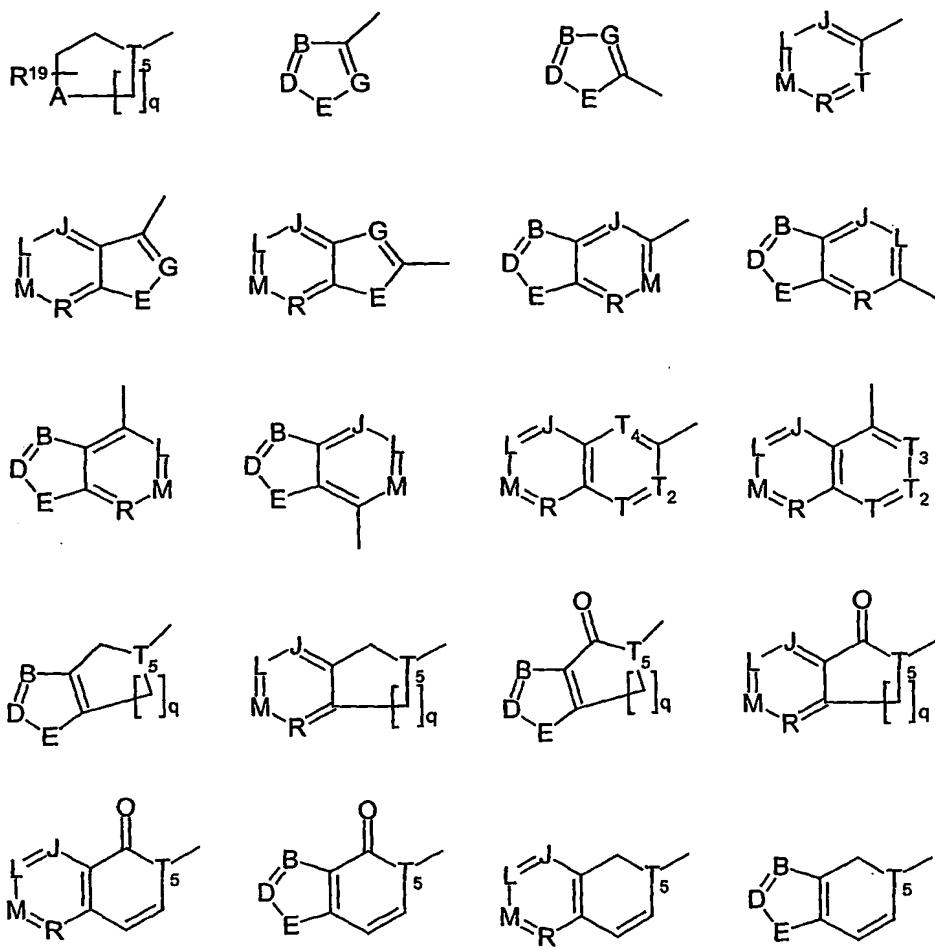
15 $Y = CR^{12}R^{13}CO$, where R^{12}, R^{13} are chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl;

20 $(X)_o = CR^{14}R^{15}$, where R^{14} and R^{15} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and $Ar-C_{0-7}$ -alkyl and o is a number from zero to three;

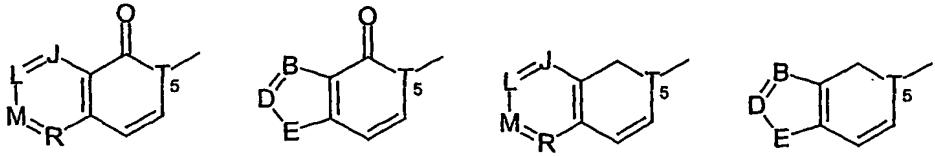
25 $(W)_n = O, S, C(O), S(O)$ or $S(O)_2$ or NR^{16} , where R^{16} is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and $Ar-C_{0-7}$ -alkyl and n is zero or one;

30 $(V)_m = C(O), C(S), S(O), S(O)_2, S(O)_2NH, OC(O), NHC(O), NHS(O), NHS(O)_2, OC(O)NH, C(O)NH$ or $CR^{17}R^{18}$, where R^{17} and R^{18} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl and m is a number from zero to three, provided that when m is greater than one, $(V)_m$ contains a maximum of one carbonyl or sulphonyl group;

U = a stable 5- to 7-membered monocyclic or a stable 8- to 11-membered bicyclic ring which is either saturated or unsaturated and which includes zero to four heteroatoms (as detailed below):



5



wherein R¹⁹ is:

C₀₋₇-alkyl, C₃₋₆-cycloalkyl, Ar-C₀₋₇-alkyl, O-C₀₋₇-alkyl, O-C₃₋₆-cycloalkyl, O-Ar-C₀₋₇-alkyl, S-C₀₋₇-alkyl, S-C₃₋₆-cycloalkyl, S-Ar-C₀₋₇-alkyl, NH-C₀₋₇-alkyl, NH-C₃₋₆-cycloalkyl, NH-Ar-C₀₋₇-alkyl, N(C₀₋₇-alkyl)₂, N(C₃₋₆-cycloalkyl)₂ or N(Ar-C₀₋₇-alkyl)₂; or, when part of a CHR¹⁹ or CR¹⁹ group, R¹⁹ may be halogen;

10

A is chosen from:

CH₂, CHR¹⁹, O, S and NR²⁰;

15

where R¹⁹ is as defined above; and R²⁰ is chosen from:

$C_{0.7}$ -alkyl, $C_{3.6}$ -cycloalkyl and Ar- $C_{0.7}$ -alkyl;

B, D and G are independently chosen from:

CR^{19} , where R^{19} is as defined above, or N;

5

E is chosen from:

CH_2 , CHR^{19} , O, S and NR^{20} , where R^{19} and R^{20} are defined as above;

J, L, M, R, T, T_2 , T_3 and T_4 are independently chosen from:

10 CR^{19} and N, where R^{19} is as defined above;

T_5 is chosen from:

CH or N;

15 q is a number from one to three, thereby defining a 5-, 6- or 7-membered ring.

B, D, G, J, L, M, R, T, T_2 , T_3 and T_4 may additionally represent an N-oxide ($N \rightarrow O$).

20 The present invention includes all salts, hydrates, solvates, complexes and prodrugs of the compounds of this invention. The term "compound" is intended to include all such salts, hydrates, solvates, complexes and prodrugs, unless the context requires otherwise.

25 Appropriate pharmaceutically and veterinarily acceptable salts of the compounds of general formulae (I) and (II) include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, 30 heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, propionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate,

ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-naphthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, 5 phosphoric and sulphonic acids. Salts which are not pharmaceutically or veterinarilly acceptable may still be valuable as intermediates.

Prodrugs are any covalently bonded compounds which release the active parent drug according to general formulae (I) or (II) *in vivo*. A prodrug may for example 10 constitute an acetal or hemiacetal derivative of the exocyclic ketone functionality present in the tetrahydrofuro[3,2-*b*]pyrrol-3-one, tetrahydrothieno[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydrocyclopenta[*b*]pyrrol-6-one, tetrahydrofuro[3,2-*c*]pyrazol-6-one, tetrahydrothieno[3,2-*c*]pyrazol-6-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one, hexahydrocyclopentapyrazol-6-one, 15 hexahydrofuro[3,2-*b*]pyridin-3-one, hexahydrothieno[3,2-*b*]pyridin-3-one, octahydropyrrolo[3,2-*b*]pyridin-3-one, octahydrocyclopenta[*b*]pyridin-7-one, hexahydrofuro[3,2-*c*]pyridazin-7-one, hexahydrothieno[3,2-*c*]pyridazin-7-one, octahydropyrrolo[3,2-*c*]pyridazin-7-one or octahydrocyclopenta[*c*]pyridazin-7-one 20 scaffold. If a chiral centre or another form of isomeric centre is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereoisomers, are intended to be covered herein. Compounds of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

25

'Halogen' as applied herein is meant to include F, Cl, Br, I;

'Heteroatom' as applied herein is meant to include O, S and N;

30 'C₀₋₇-alkyl' as applied herein is meant to include stable straight and branched chain aliphatic carbon chains containing zero (*i.e.* simply hydrogen) to seven carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl,

isopentyl, hexyl, heptyl and any simple isomers thereof. Additionally, any C₀₋₇-alkyl may optionally be substituted at any point by one, two or three halogen atoms (as defined above) for example to give a trifluoromethyl substituent. Furthermore, C₀₋₇-alkyl may contain one or more heteroatoms (as defined above) for example to give
5 ethers, thioethers, sulphones, sulphonamides, substituted amines, amidines, guanidines, carboxylic acids, carboxamides. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or two hydrogen atoms. A heteroatom or halogen is only present when C₀₋₇-alkyl contains a minimum of one carbon atom.

10

‘C₃₋₆-cycloalkyl’ as applied herein is meant to include any variation of ‘C₀₋₇-alkyl’ which additionally contains a carbocyclic ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. The carbocyclic ring may optionally be substituted with one or more halogens (as defined above) or heteroatoms (as defined above) for example
15 to give a tetrahydrofuran, pyrrolidine, piperidine, piperazine or morpholine substituent.

‘Ar-C₀₋₇-alkyl’ as applied herein is meant to include any variation of C₀₋₇-alkyl which
20 additionally contains an aromatic ring moiety ‘Ar’. The aromatic ring moiety Ar can be a stable 5 or 6-membered monocyclic or a stable 9 or 10 membered bicyclic ring which is unsaturated, as defined previously for U in general formulae (I) and (II). The aromatic ring moiety Ar may be substituted by R¹⁹ (as defined above for U in general formulae (I) and (II)). When C = 0 in the substituent Ar-C₀₋₇-alkyl, the substituent is simply the aromatic ring moiety Ar.

25

Other expressions containing terms such as alkyl and cycloalkyl are intended to be construed according to the definitions above. For example “C₁₋₄ alkyl” is the same as C₀₋₇-alkyl except that it contains from one to four carbon atoms.

30 If different structural isomers are present, and/or one or more chiral centres are present, all isomeric forms are intended to be covered. Enantiomers are characterised by the absolute configuration of their chiral centres and described by the R- and S-

sequencing rules of Cahn, Ingold and Prelog. Such conventions are well known in the art (e.g. see 'Advanced Organic Chemistry', 3rd edition, ed. March, J., John Wiley and Sons, New York, 1985).

5 Preferred compounds of general formulae (I) and (II) include, but are not limited to, those in which, independently or in combination:

Z is O, S, NH or CH₂;

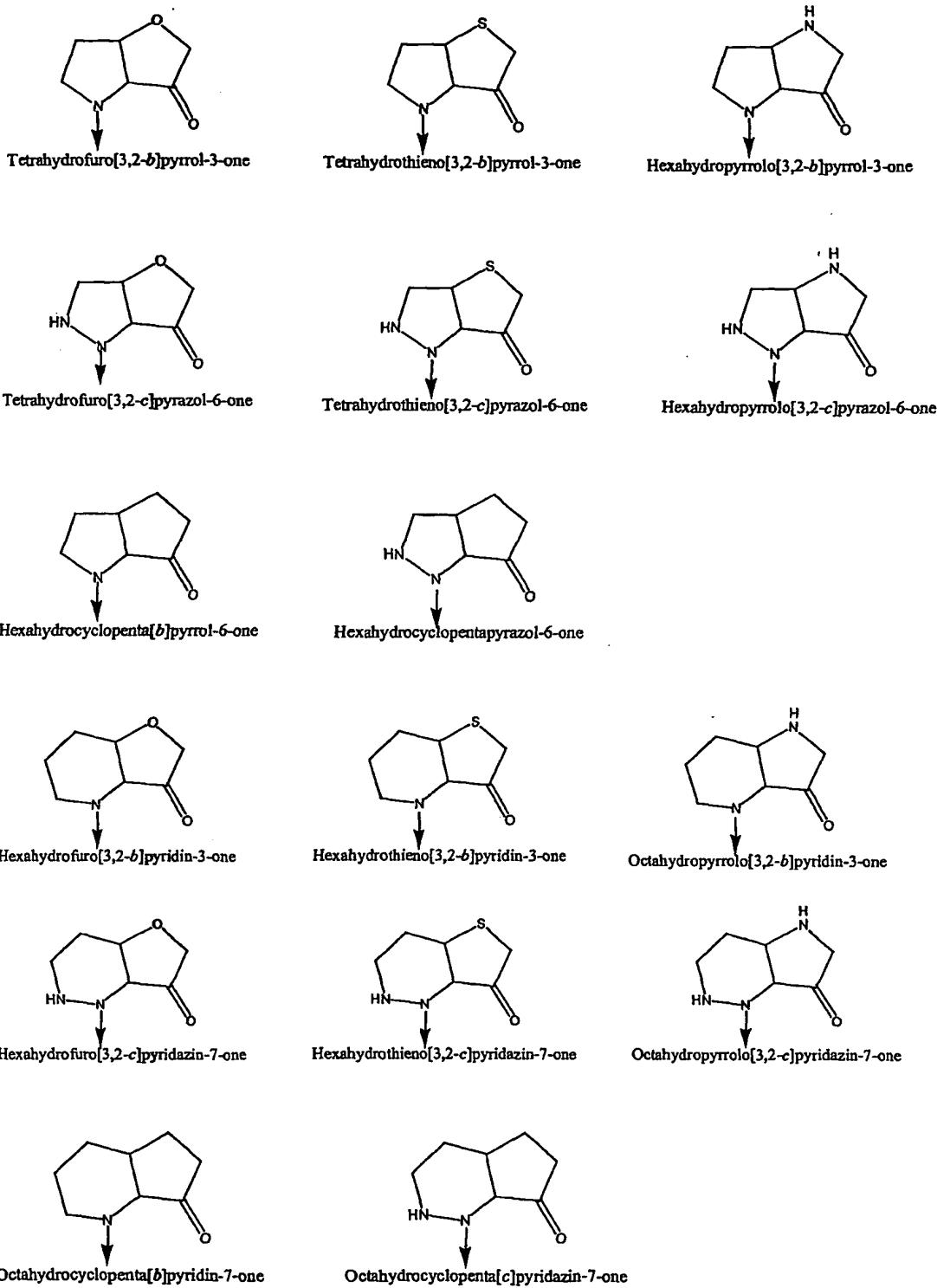
P¹ and P² are CH₂; and

10 Q is CH₂ or NH.

Also, preferred compounds of general formulae (I) and (II) include, but are not limited to, those in which, independently or in combination

15 Z is NR⁴, where R⁴ is a Ar-C₁₋₄-alkyl or a substituted carbonyl or sulphonyl group;
P¹ and P² are CH₂; and
Q is CH₂ or NH.

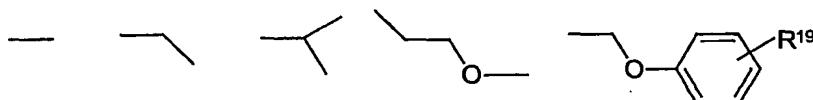
Thus, examples of preferred compounds include those containing a bicyclic moiety chosen from tetrahydrofuro[3,2-*b*]pyrrol-3-one, tetrahydrothieno[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydrocyclopenta[*b*]pyrrol-6-one, tetrahydrofuro[3,2-*c*]pyrazol-6-one, tetrahydro-thieno[3,2-*c*]pyrazol-6-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one, hexahydro-cyclo-pentapyrazol-6-one, hexahydrofuro[3,2-*b*]pyridin-3-one, hexahydrothieno[3,2-*b*]pyridin-3-one, 25 octahydropyrrolo[3,2-*b*]pyridin-3-one, octahydrocyclopenta[*b*]pyridin-7-one, hexahydrofuro[3,2-*c*]pyridazin-7-one, hexahydrothieno[3,2-*c*]pyridazin-7-one, octahydropyrrolo[3,2-*c*]pyridazin-7-one or octahydrocyclopenta[*c*]pyridazin-7-one as shown below.



In compounds of general formulae (I) and (II), it is preferred that R^1 comprises C_{0-7} -alkyl or $Ar-C_{0-7}$ -alkyl. Thus, for example, preferred R^1 moieties include hydrogen, or a straight or branched alkyl chain, or a straight or branched heteroalkyl chain, or an optionally substituted arylalkyl chain, or an optionally substituted arylheteroalkyl chain.

5

10



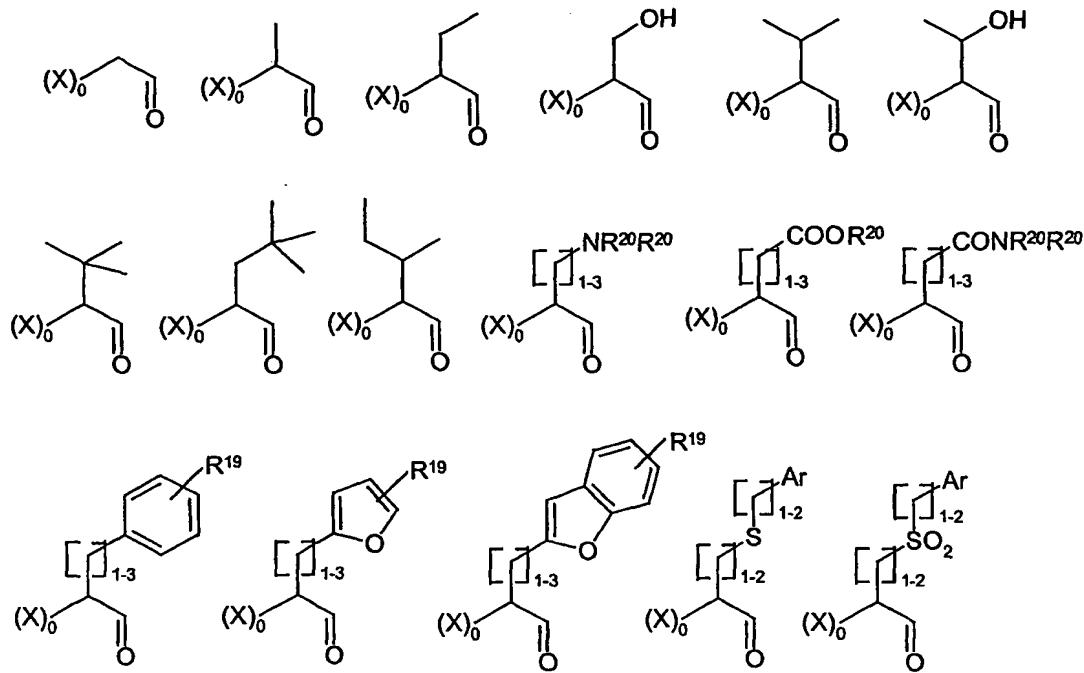
where R^{19} is defined above.

In preferred compounds of general formulae (I) and (II), Y is $CHR^{13}CO$ where R^{13} is selected from C_{0-7} -alkyl or $Ar-C_{0-7}$ -alkyl, for example hydrogen, a straight or branched alkyl chain, a straight or branched heteroalkyl chain, an optionally substituted arylalkyl chain or an optionally substituted arylheteroalkyl chain. Additionally, in preferred compounds of general formulae (I) and (II), R^{13} is selected from C_{3-6} -cycloalkyl, for example cyclohexylmethyl.

20

Examples of preferred Y substituents include the following:

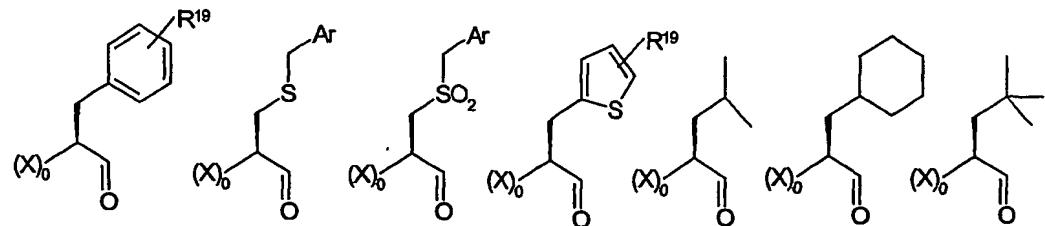
-16-



wherein R^{19} , R^{20} and Ar are as defined above.

5 More preferred R^{13} groups include C_{1-4} -alkyl, which may be substituted with OH , $NR^{20}R^{20}$, $COOR^{20}$, or $CONR^{20}$ or cycloalkylmethyl or $Ar-C_{1-4}$ -alkyl, where the aryl group may be substituted with R^{19} ; wherein each R^{19} and R^{20} is independently as defined above.

10 Even more preferred R^{13} groups comprise $Ar-CH_2-$, where the aromatic ring is an optionally substituted phenyl or monocyclic heterocycle. Additionally, even more preferred R^{13} groups comprise simple branched alkyl groups such as isobutyl or straight heteroalkyl chains such as benzylsulfanylmethyl or benzylsulphonylmethyl. Furthermore, even more preferred R^{13} groups comprise cyclohexylmethyl. Examples 15 of even more preferred Y substituents comprise the following,

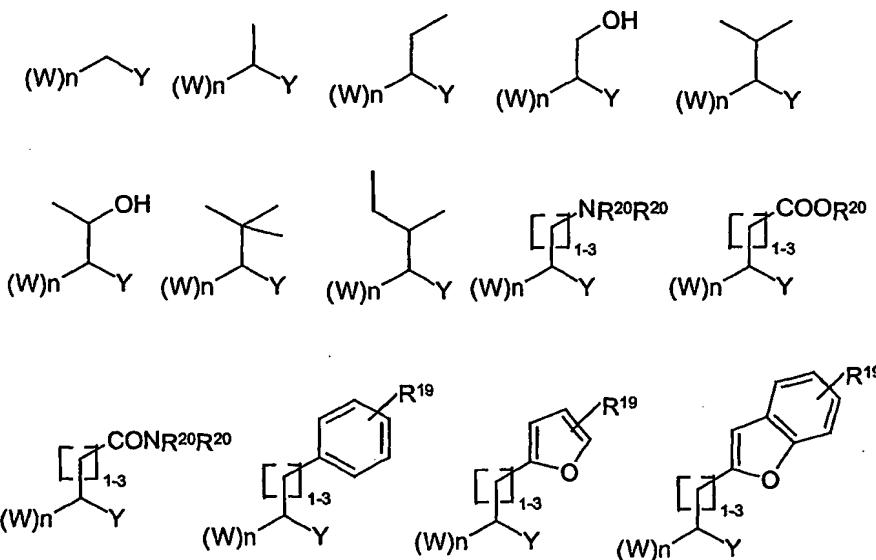


wherein R¹⁹ and Ar are as defined previously

It is preferred that in the group (X)_o, each of R¹⁴ and R¹⁵ is selected from C₀₋₇-alkyl or Ar-C₀₋₇-alkyl, for example hydrogen, a straight or branched alkyl chain, a straight or branched heteroalkyl chain, an optionally substituted arylalkyl chain or an optionally substituted arylheteroalkyl chain.

More preferred (X)_o groups comprise R¹⁴ chosen from hydrogen; R¹⁵ is C₁₋₄-alkyl, which may be substituted with OH, NR²⁰R²⁰, COOR²⁰, or CONR²⁰; or Ar-C₁₋₄-alkyl, where the aryl group may be substituted with R¹⁹, wherein each R¹⁹ and R²⁰ is independently as defined above.

Examples of preferred (X)_o groups include the following:



wherein R¹⁹ and R²⁰ are as defined previously.

Even more preferred compounds of general formulae (I) and (II), comprise (X)_o groups that are simple alkyl groups such as methylene and where o = 0 or 1.

In the group (W)_n, W is preferably O, S, SO₂, S(O), C(O) or NR¹⁶, where R¹⁶ is C₀₋₄-alkyl; and n is 0 or 1.

More preferred compounds of general formulae (I) and (II), comprise $(W)_n$ groups defined as O, S, SO_2 , $C(O)$ and NH where $n = 0$ or 1.

Yet even more preferred compounds of general formulae (I) and (II), comprise $(W)_n$

5 groups defined as NH where $n = 1$.

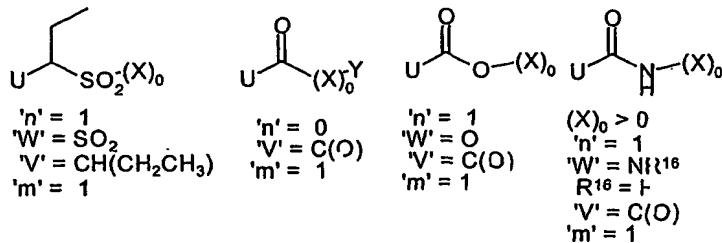
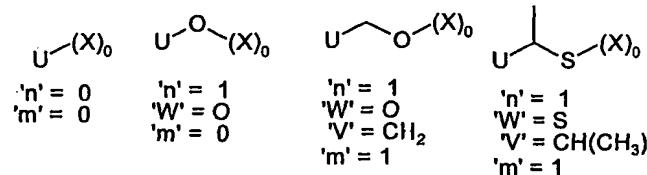
In the group $(V)_m$:

V is preferably $C(O)$, $C(O)NH$ or CHR^{18} , where R^{18} is C_{0-4} -alkyl; and

m is 0 or 1.

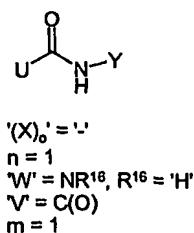
10

Preferred V and W substituent combinations encompassed by general formulae (I) and (II) include, but are not limited to:

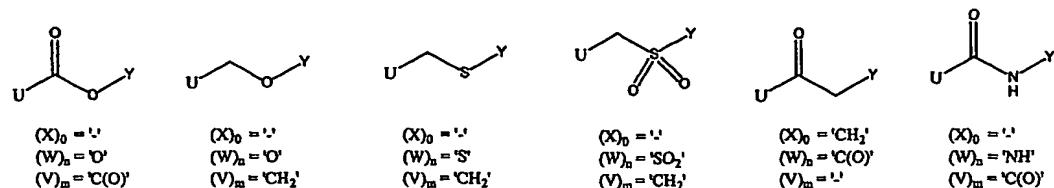


15

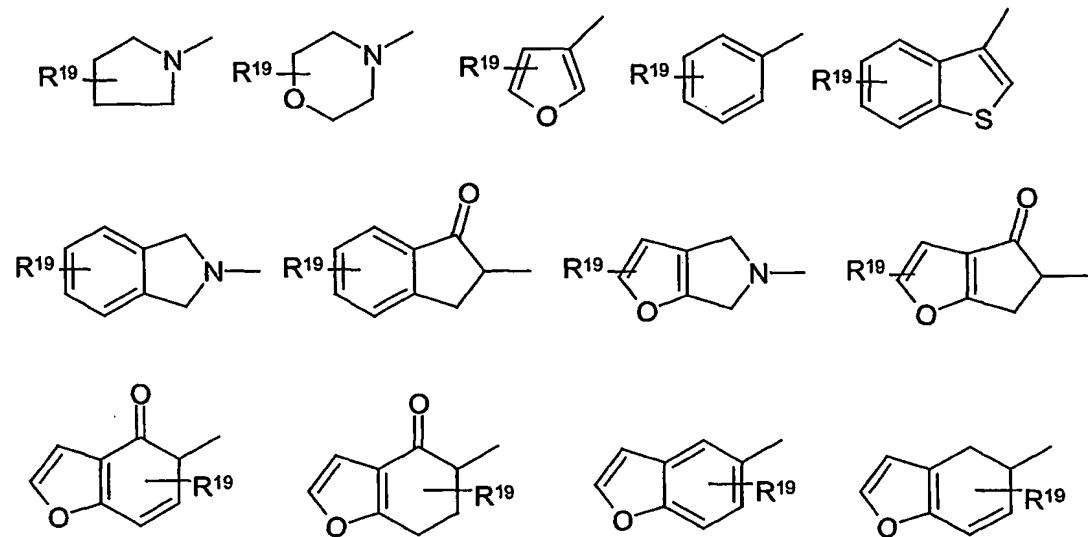
Additionally, a preferred V and W substituent combination encompassed by general formulae (I) and (II) includes, but is not limited to:



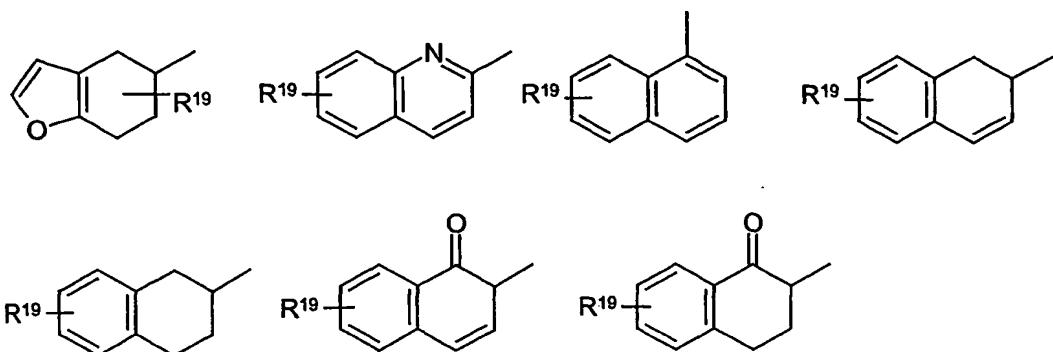
More preferred V, W and X substituent combinations encompassed by general formulae (I) and (II) comprise, but are not limited to



5 In preferred compounds of general formulae (I) and (II), U comprises an optionally substituted 5- or 6-membered saturated or unsaturated heterocycle or Ar group or an optionally substituted saturated or unsaturated 9- or 10-membered heterocycle or Ar group. Examples of such preferred U rings include the following:

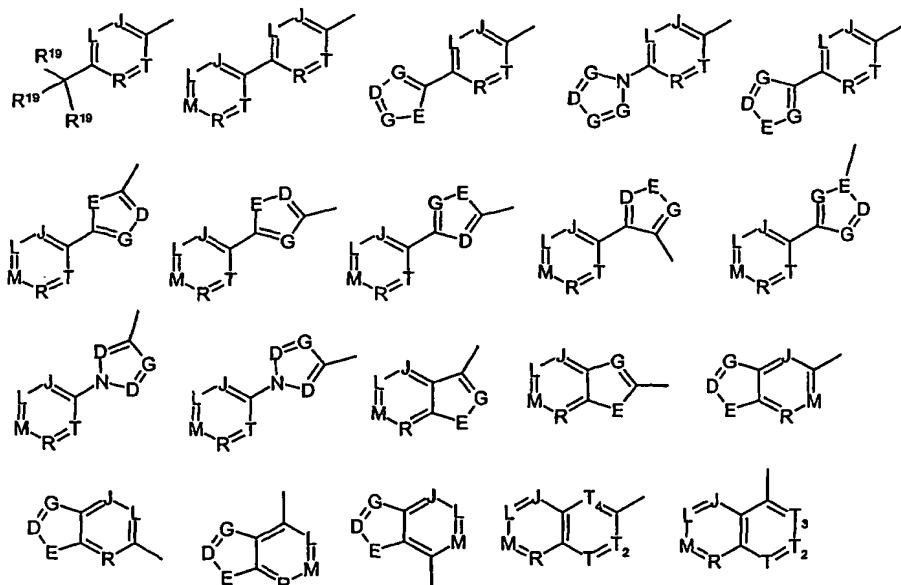


and also the following



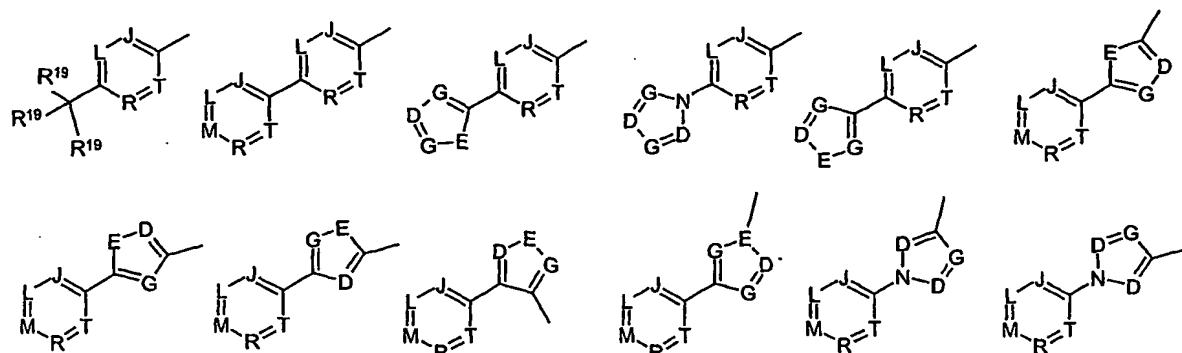
wherein R^{19} is as defined previously.

More preferred compounds of general formulae (I) and (III), contain a U group comprising of a bulky alkyl or aryl group at the para position of an aryl Ar. Also, more preferred compounds contain a meta or para-biaryl Ar-Ar, where Ar is as previously defined. Additionally, more preferred compounds contain a 6,6 or 6,5 or 5,6-fused aromatic ring. Examples of more preferred U groups are



wherein R^{19} , D, E, G, J, L, M, R, T, T_2 , T_3 and T_4 are as defined previously.

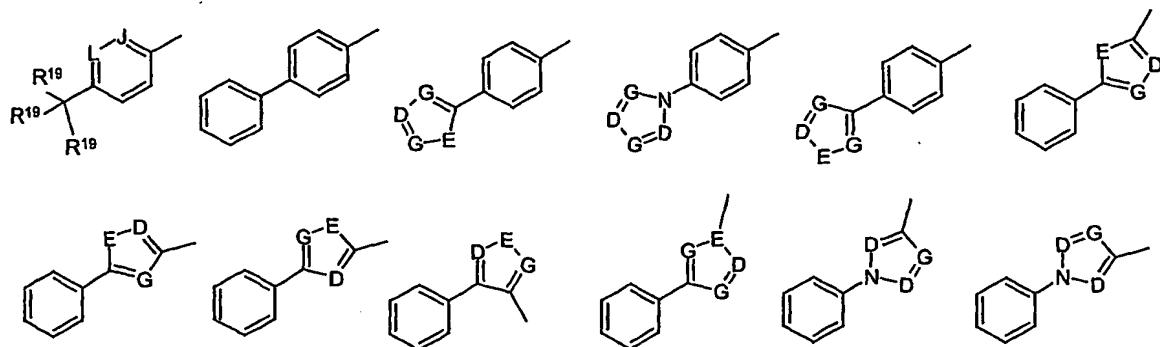
Even more preferred compounds of general formulae (I) and (II), particularly for inhibition of cruzipain, contain a U group comprising a 6-membered Ar ring containing a bulky alkyl or aryl group at the para position, where Ar is as previously defined



5

wherein R¹⁹, D, E, G, J, L, M, R and T are as defined previously

Yet even more preferred compounds of general formulae (I) and (II), contain a U
10 group comprising but are not limited to the following,

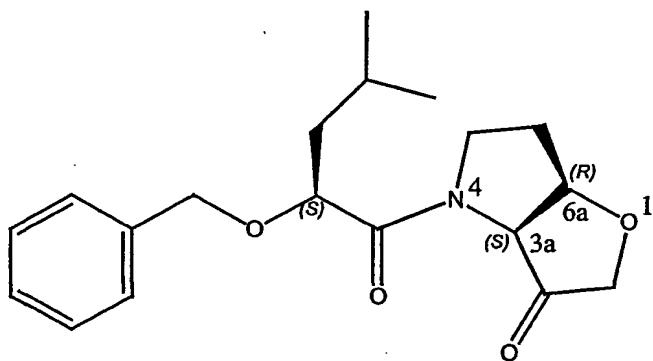


wherein R¹⁹, D, E, G, J and L are as defined previously.

15

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe compounds of the present invention, following the general

guidelines presented by the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9-, 1984. Compounds of formulae (I) and (II) and the intermediates and starting materials used in their preparation are named in accordance with the IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group. An example compound of formula (I), compound (1) in which R¹ is H, P₁ is methylene, Q is methylene, Z is oxygen, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

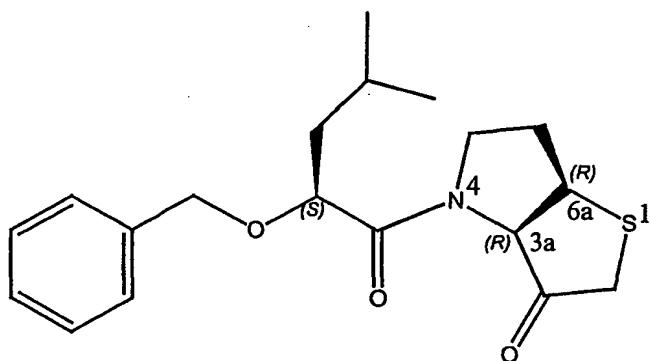


10

(1)

(3aS,6aR) 4-(2S-Benzylxy-4-methylpentanoyl)tetrahydrofuro[3,2-b]pyrrol-3-one

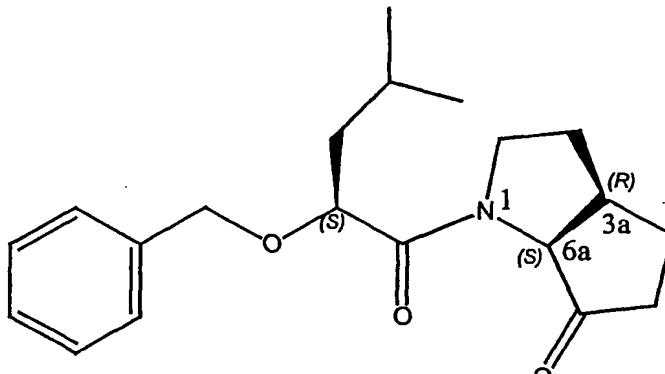
A second example compound of formula (I), compound (2) in which R¹ is H, P₁ is methylene, Q is methylene, Z is sulphur, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-



(2)

20 (3aR,6aR) 4-(2S-Benzylxy-4-methylpentanoyl)tetrahydrothieno[3,2-b]pyrrol-3-one

A third example compound of formula (I), compound (3) in R^1 is H, P_1 is methylene, Q is methylene, Z is methylene, Y is 4-methylpentyl, $(X)_0$ is zero, $(W)_n$ is oxygen, $(V)_m$ is methylene and U is phenyl is thus named:-

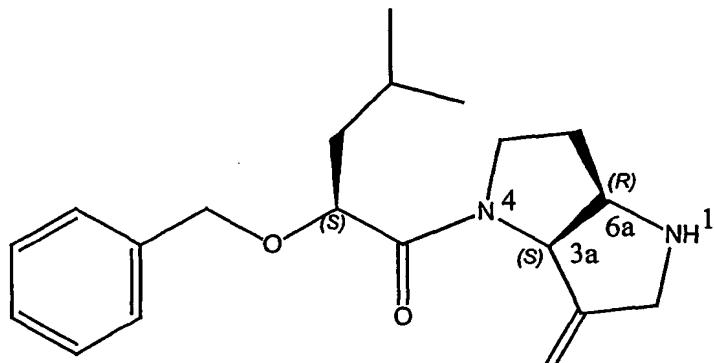


5

(3)

(3a*R*,6a*S*) 1-(2*S*-Benzylxy-4-methylpentanoyl)hexahydrocyclopenta[*b*]pyrrol-6-one

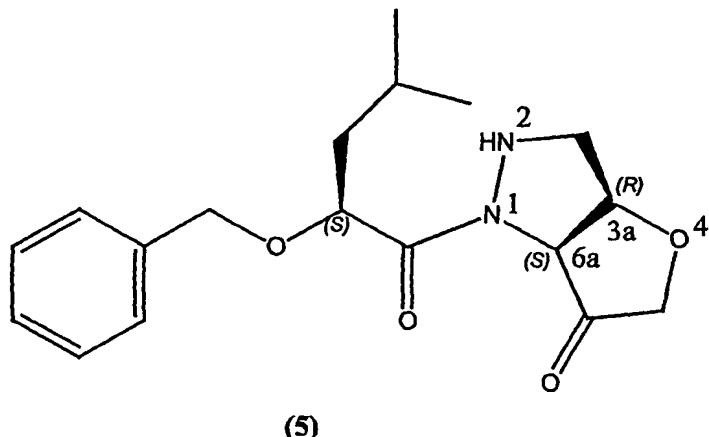
A fourth example compound of formula (I), compound (4) in R^1 is H, P_1 is methylene, Q is methylene, Z is NH, Y is 4-methylpentyl, $(X)_0$ is zero, $(W)_n$ is oxygen, $(V)_m$ is methylene and U is phenyl is thus named:-



(4)

(3a*S*,6a*R*) 1-(2*S*-Benzylxy-4-methylpentanoyl)hexahdropyrrolo[3,2-*b*]pyrrol-3-one

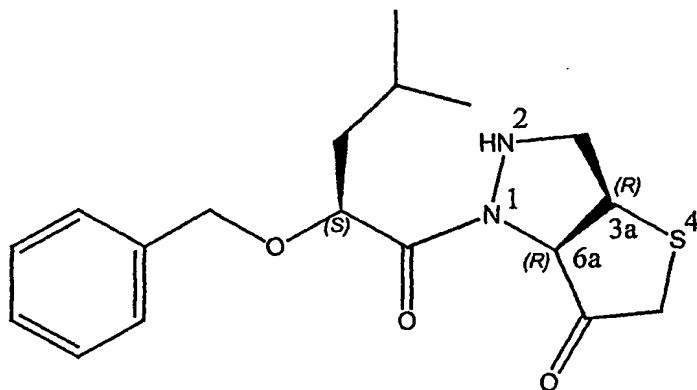
15 A fifth example compound of formula (I), compound (5) in which R^1 is H, P_1 is methylene, Q is NH, Z is oxygen, Y is 4-methylpentyl, $(X)_0$ is zero, $(W)_n$ is oxygen, $(V)_m$ is methylene and U is phenyl is thus named:-



(3aR,6aS) 4-(2S-Benzyl-4-methylpentanoyl)tetrahydrofuro[3,2-c]pyrazol-6-one

5

A sixth example compound of formula (I), compound (6) in which R¹ is H, P₁ is methylene, Q is NH, Z is sulphur, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

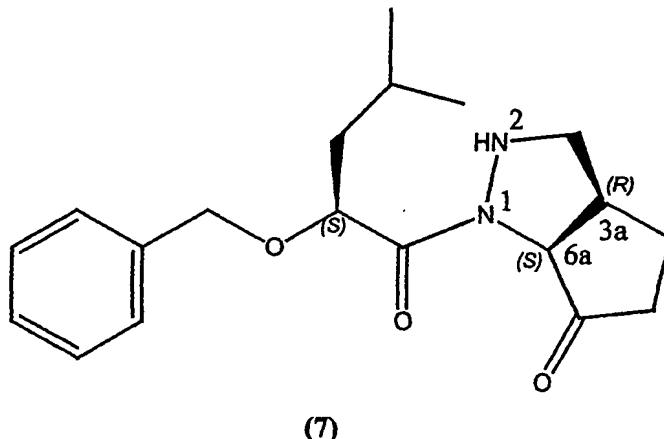


(3aR,6aR) 4-(2S-Benzyl-4-methylpentanoyl)tetrahydrothieno[3,2-c]pyrazol-6-one

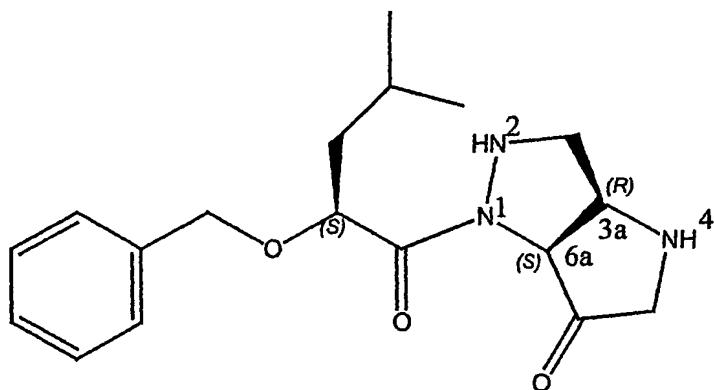
10

15 A seventh example compound of formula (I), compound (7) in R¹ is H, P₁ is methylene, Q is NH, Z is methylene, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

-25-

(3a*R*,6a*S*) 1-(2*S*-Benzylxy-4-methylpentanoyl)hexahydrocyclopentapyrazol-6-one

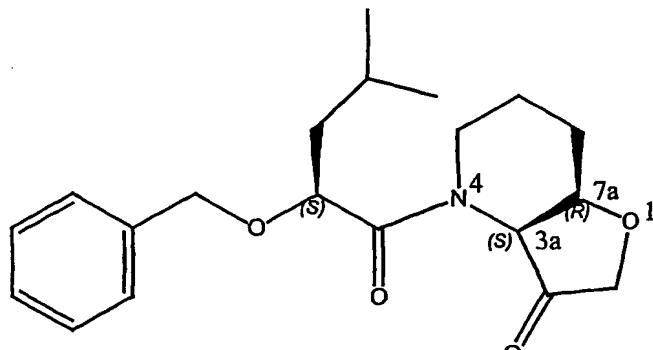
5 An eighth example compound of formula (I), compound (8) in R^1 is H, P_1 is methylene, Q is NH, Z is NH, Y is 4-methylpentyl, $(X)_0$ is zero, $(W)_n$ is oxygen, $(V)_m$ is methylene and U is phenyl is thus named:-



(8)

10 (3a*R*,6a*S*) 1-(2*S*-Benzylxy-4-methylpentanoyl)hexahdropyrrolo[3,2-c]pyrazol-6-one

15 An example compound of formula (II), compound (9) in which R^1 is H, P_1 is methylene, P_2 is methylene, Q is methylene, Z is oxygen, Y is 4-methylpentyl, $(X)_0$ is zero, $(W)_n$ is oxygen, $(V)_m$ is methylene and U is phenyl is thus named:-

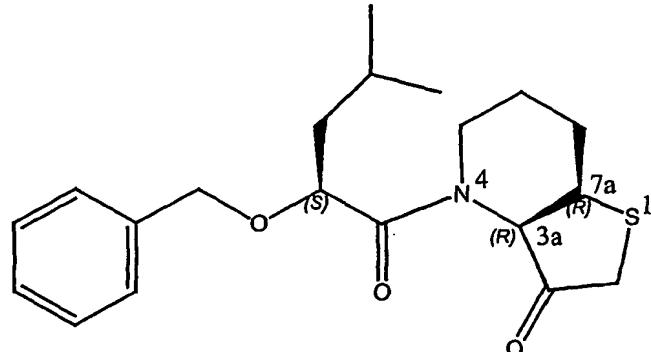


(9)

(3a*S*,7a*R*) 4-(2*S*-Benzylxy-4-methylpentanoyl)hexahydrofuro[3,2-*b*]pyridin-3-one

5

A second example compound of formula (II), compound (10) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is methylene, Z is sulphur, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-



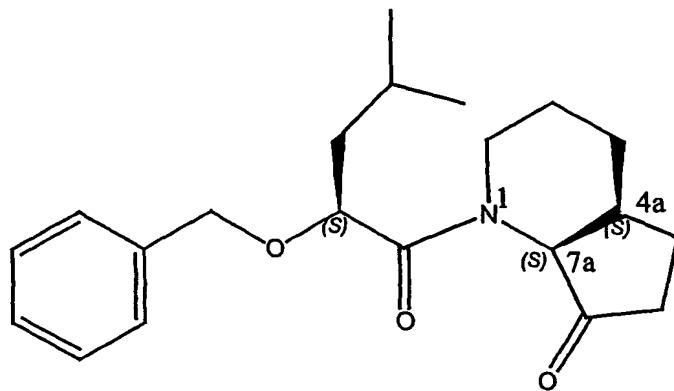
10

(10)

(3a*R*,7a*R*) 4-(2*S*-Benzylxy-4-methylpentanoyl)hexahydrothieno[3,2-*b*]pyridin-3-one

15

A third example compound of formula (II), compound (11) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is methylene, Z is methylene, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-



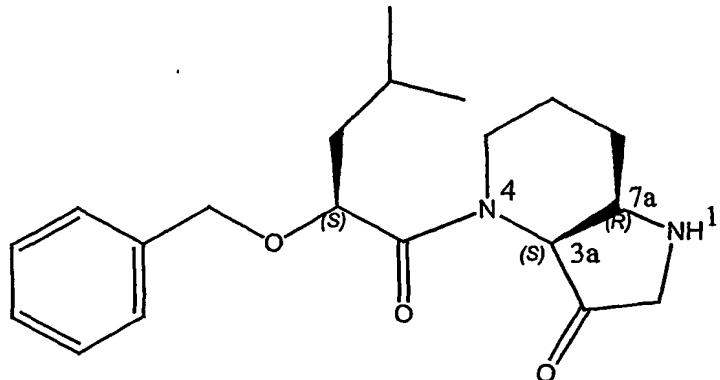
(11)

(4a*S*,7a*S*) 1-(2*S*-Benzylxy-4-methylpentanoyl)octahydrocyclopenta[*b*]pyridin-7-one

5

A fourth example compound of formula (II), compound (12) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is methylene, Z is NH, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

10



(12)

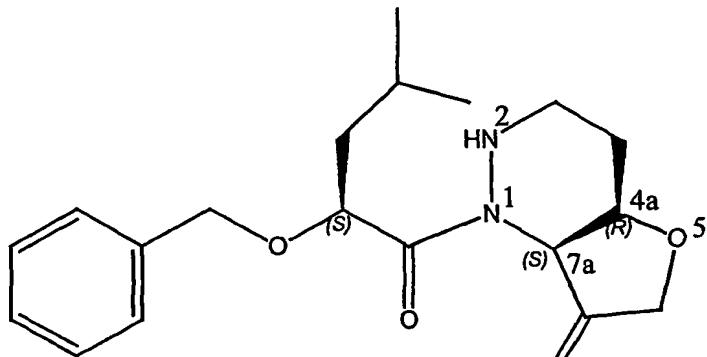
(3a*S*,7a*R*) 4-(2*S*-Benzylxy-4-methylpentanoyl)octahydropyrrolo[3,2-*b*]pyridin-3-one

15

A fifth example compound of formula (II), compound (13) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is NH, Z is oxygen, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

20

-28-

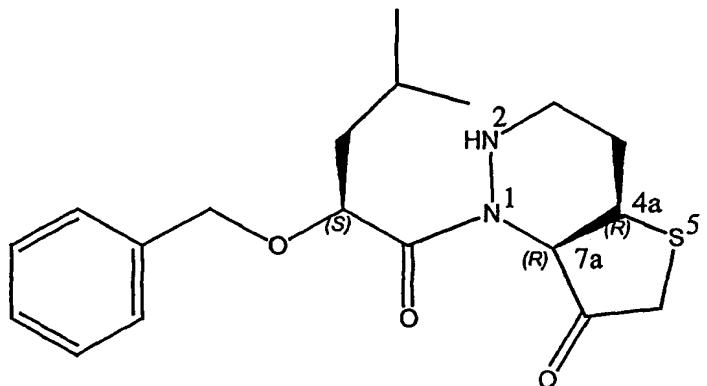


(13)

(4aR,7aS) 4-(2S-Benzylxy-4-methylpentanoyl)hexahydrofuro[3,2-c]pyridazin-7-one

5

A sixth example compound of formula (II), compound (14) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is NH, Z is sulphur, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

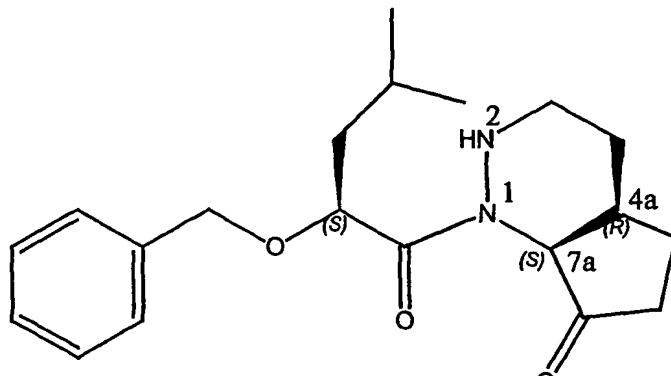


(14)

(4aR,7aR) 4-(2S-Benzylxy-4-methylpentanoyl)hexahydrofuro[3,2-c]pyridazin-7-one

10

A seventh example compound of formula (II), compound (15) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is NH, Z is methylene, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-

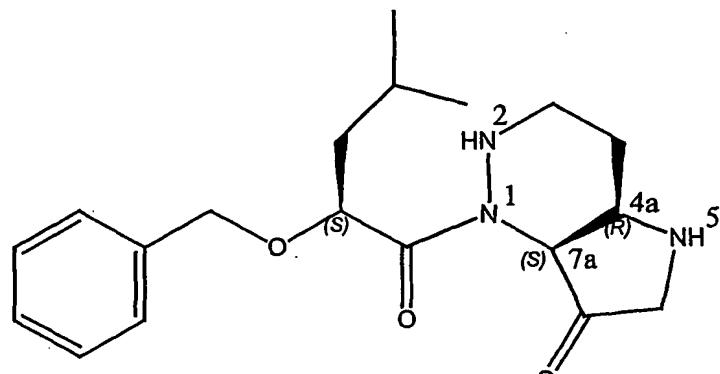


(15)

(4a*R*,7a*S*) 4-(2*S*-Benzylxy-4-methylpentanoyl)octahydrocyclopenta[*c*]pyridazin-7-one

5

An eighth example compound of formula (II), compound (16) in which R¹ is H, P₁ is methylene, P₂ is methylene, Q is NH, Z is NH, Y is 4-methylpentyl, (X)₀ is zero, (W)_n is oxygen, (V)_m is methylene and U is phenyl is thus named:-



10

(16)

(4a*R*,7a*S*) 4-(2*S*-Benzylxy-4-methylpentanoyl)octahydropyrrolo[3,2-*c*]pyridazin-7-one

15

Compounds of the invention include, but are not limited to, the following examples that are the (3a*S*, 6a*R*) isomer of general formula (I), where Z = 'O' and R¹ = 'H', and also include the equivalent analogues included in the full definition of Z and R¹

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 4-*tert*-Butyl-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

10 4-Dimethylamino-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-isopropylbenzamide

15 4-Difluoromethoxy-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

20 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

25 3-Bromo-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

30 Naphthalene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Quinoline-6-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Benzo[*b*]thiophene-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzothiazole-5-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Biphenyl-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxybenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxybenzamide

25 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-imidazol-1-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

30 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

5 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

10 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenylnicotinamide

15 2-Phenylthiazole-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 5-Phenylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 2-Methyl-5-phenylfuran-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 4-Phenylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-

5 hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 3-Phenylpyrrole-1-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

15 4-*tert*-Butyl-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-trifluoromethoxybenzamide

20 4-Dimethylamino-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

25 4-Isopropyl-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

4-Difluoromethoxy-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

30 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

3-Bromo-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

5 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-vinylbenzamide

10 Naphthalene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

Naphthalene-1-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

15 Quinoline-6-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

20 Benzo[*b*]thiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

25 Benzothiazole-5-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

Biphenyl-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

30 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-phenoxybenzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-3-phenoxy benzamide

5 4-Imidazol-1-yl-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-thiophen-2-ylbenzamide

10 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-oxazol-5-ylbenzamide

15 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-[1,2,3]thiadiazol-4-ylbenzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-pyrazol-1-ylbenzamide

20 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-5-thiophen-2-ylnicotinamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-6-phenylnicotinamide

25 2-Phenylthiazole-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

30 2-Pyridin-3-ylthiazole-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

5-Phenylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]

5 pyrrole-4-carbonyl) butyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

10 4-Phenylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

15

2-Thiophen-2-ylthiazole-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

20 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

3-Phenylpyrrole-1-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

25 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

4-*tert*-Butyl-*N*-[1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

30

N-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

4-Dimethylamino-*N*-[1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-isopropylbenzamide

4-Difluoromethoxy-*N*-[1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

10 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

15 4-Bromo-*N*-[1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

3-Bromo-*N*-[1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

20 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

Naphthalene-2-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Naphthalene-1-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Quinoline-6-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexa-

5 hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzothiazole-5-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Biphenyl-4-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxybenzamide

15 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxybenzamide

20 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-imidazol-1-ylbenzamide

N-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

25 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

N-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

30 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

N-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

5 *N*-[1-(3-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenylnicotinamide

2-Phenylthiazole-4-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 5-Phenylthiophene-2-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 2-Methyl-5-phenylfuran-3-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Phenylthiophene-2-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

3-Phenylpyrrole-1-carboxylic acid [1-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydro

5 furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]benzamide

10 4-*tert*-Butyl-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]benzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-trifluoromethoxybenzamide

15 4-Dimethylamino-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]benzamide

20 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-isopropylbenzamide

4-Difluoromethoxy-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]benzamide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]benzamide

30 3-Bromo-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]benzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-vinylbenzamide

5 Naphthalene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

Naphthalene-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

10 Quinoline-6-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

15 Benzo[*b*]thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

20 Benzothiazole-5-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

Biphenyl-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-phenoxybenzamide

30 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-3-phenoxybenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-imidazol-1-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-

5 thiophen-2-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-oxazol-5-ylbenzamide

10 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-4-pyrazol-1-ylbenzamide

15 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-5-thiophen-2-ylnicotinamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]-6-

20 phenylnicotinamide

2-Phenylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

25 2-Pyridin-3-ylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

5-Phenylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

30 5-Pyridin-3-ylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

5 4-Phenylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

10 2-Thiophen-2-ylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

15 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

3-Phenylpyrrole-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-4-ylmethylethyl]amide

20 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]benzamide

4-*tert*-Butyl-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]benzamide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-trifluoromethoxybenzamide

30 4-Dimethylamino-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]benzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-isopropylbenzamide

5 4-Difluoromethoxy-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]benzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-trifluoromethylbenzamide

10 4-Bromo-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]benzamide

3-Bromo-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]benzamide

15 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-vinylbenzamide

20 Naphthalene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

Naphthalene-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

25 Quinoline-6-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

30 Benzo[*b*]thiophene-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

Benzothiazole-5-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

5 Biphenyl-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-phenoxybenzamide

10 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-3-phenoxybenzamide

15 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-imidazol-1-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-thiophen-2-ylbenzamide

20 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-oxazol-5-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-4-pyrazol-1-ylbenzamide

30 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-5-thiophen-2-ylnicotinamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]-6-phenylnicotinamide

5 2-Phenylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

2-Pyridin-3-ylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

10 5-Phenylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

15 5-Pyridin-3-ylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

20 4-Phenylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

25 2-Thiophen-2-ylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

30 3-Phenylpyrrole-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-pyridin-3-ylmethylethyl]amide

N-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 4-*tert*-Butyl-*N*-[1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

10 4-Dimethylamino-*N*-[1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

15 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-isopropylbenzamide

4-Difluoromethoxy-*N*-[1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

20 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

25 3-Bromo-*N*-[1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

30 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

Naphthalene-2-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Quinoline-6-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Benzo[*b*]thiophene-2-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Benzothiazole-5-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Biphenyl-4-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxybenzamide

25 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxybenzamide

30 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-imidazol-1-ylbenzamide

N-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

N-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

5 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

N-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

10 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

15 *N*-[1-(4-Bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenylnicotinamide

2-Phenylthiazole-4-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Phenylthiophene-2-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 2-Methyl-5-phenylfuran-3-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Phenylthiophene-2-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(4-bromobenzyl)-2- oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

3-Phenylpyrrole-1-carboxylic acid [1-(4-bromobenzyl)-2-oxo-2-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 *N*-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4- yl)ethyl]benzamide

20 4-*tert*-Butyl-*N*-[1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4- yl)ethyl]benzamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- trifluoromethoxybenzamide

25 4-Dimethylamino-*N*-[1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2- *b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- isopropylbenzamide

30 4-Difluoromethoxy-*N*-[1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2- *b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

5 4-Bromo-*N*-[1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

3-Bromo-*N*-[1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

10 *N*-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

15 Naphthalene-2-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Quinoline-6-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Benzo[*b*]thiophene-2-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 Benzothiazole-5-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Biphenyl-4-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

5 phenoxybenzamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-

phenoxybenzamide

10 *N*-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

imidazol-1-ylbenzamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

thiophen-2-ylbenzamide

15 *N*-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

oxazol-5-ylbenzamide

20 *N*-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

[1,2,3]thiadiazol-5-ylbenzamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

pyrazol-1-ylbenzamide

25 *N*-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-

thiophen-2-ylnicotinamide

N-[1-(4-Fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-

phenylnicotinamide

30 2-Phenylthiazole-4-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexa-

hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 5-Phenylthiophene-2-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 2-Methyl-5-phenylfuran-3-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 4-Phenylthiophene-2-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(4-fluorobenzyl)-2- oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 3-Phenylpyrrole-1-carboxylic acid [1-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl] benzamide

4-*tert*-Butyl-*N*-[1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

trifluoromethoxybenzamide

10 4-Dimethylamino-*N*-[1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

15 10 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-isopropylbenzamide

15 15 4-Difluoromethoxy-*N*-[1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

20 15 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

20 20 4-Bromo-*N*-[1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

25 25 3-Bromo-*N*-[1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

30 25 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

30 30 Naphthalene-2-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 30 Naphthalene-1-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Quinoline-6-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 Benzo[*b*]thiophene-2-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Benzothiazole-5-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Biphenyl-4-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- phenoxybenzamide

20 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3- phenoxybenzamide

N-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- imidazol-1-ylbenzamide

25 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- thiophen-2-ylbenzamide

30 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- oxazol-5-ylbenzamide

15 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

5 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

10 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

15 *N*-[1-(4-Chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenylnicotinamide

20 2-Phenylthiazole-4-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 5-Phenylthiophene-2-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

35 5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

40 2-Methyl-5-phenylfuran-3-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

45 4-Phenylthiophene-2-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

50 4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

3-Phenylpyrrole-1-carboxylic acid [1-(4-chlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

15 4-*tert*-Butyl-*N*-[1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

20 4-Dimethylamino-*N*-[1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-isopropylbenzamide

25 4-Difluoromethoxy-*N*-[1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

30 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

3-Bromo-*N*-[1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-

5 yl)ethyl]benzamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

10 Naphthalene-2-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Quinoline-6-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Benzo[*b*]thiophene-2-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Benzothiazole-5-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

Biphenyl-4-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl]amide

30 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxybenzamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxybenzamide

5 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-imidazol-1-ylbenzamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

10 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

15 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

20 *N*-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

N-[1-(3,4-Dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenylnicotinamide

25 2-Phenylthiazole-4-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Phenylthiophene-2-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-5 hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 4-Phenylthiophene-2-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

3-Phenylpyrrole-1-carboxylic acid [1-(3,4-dichlorobenzyl)-2-oxo-2-(3-oxo- hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl] benzamide

4-*tert*-Butyl-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2- ylmethylethyl]benzamide

30 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]- 4-trifluoromethoxybenzamide

4-Dimethylamino-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]benzamide

5 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-isopropylbenzamide

4-Difluoromethoxy-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]benzamide

10 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-trifluoromethylbenzamide

15 4-Bromo-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]benzamide

3-Bromo-*N*-[2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]benzamide

20 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-vinylbenzamide

Naphthalene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

25 Naphthalene-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

Quinoline-6-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-

5 4-yl)-1-thiophen-2-ylmethylethyl]amide

Benzothiazole-5-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

10 Biphenyl-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-phenoxybenzamide

15 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-3-phenoxybenzamide

20 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-imidazol-1-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-thiophen-2-ylbenzamide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-oxazol-5-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

30 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-4-pyrazol-1-ylbenzamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-5-thiophen-2-ylnicotinamide

5 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]-6-phenylnicotinamide

2-Phenylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

10 2-Pyridin-3-ylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

15 5-Phenylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

20 2-Methyl-5-phenylfuran-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

4-Phenylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

25 4-Pyridin-3-ylthiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

30 2-Thiophen-2-ylthiazole-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [2-oxo-2-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrol-4-yl)-1-thiophen-2-ylmethylethyl]amide

3-Phenylpyrrole-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-

5 yl)-1-thiophen-2-ylmethylethyl]amide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl] benzamide

10 4-*tert*-Butyl-*N*-[1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4- yl)ethyl]benzamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- trifluoromethoxybenzamide

15 4-Dimethylamino-*N*-[1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2- *b*]pyrrol-4-yl)ethyl]benzamide

20 *N*-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- isopropylbenzamide

4-Difluoromethoxy-*N*-[1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2- *b*]pyrrol-4-yl)ethyl]benzamide

25 *N*-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4- trifluoromethylbenzamide

4-Bromo-*N*-[1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4- yl)ethyl]benzamide

30 3-Bromo-*N*-[1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4- yl)ethyl]benzamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

5 Naphthalene-2-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Quinoline-6-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Benzo[*b*]thiophene-2-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Benzothiazole-5-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Biphenyl-4-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 *N*-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxybenzamide

30 *N*-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxybenzamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-imidazol-1-ylbenzamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-

5 thiophen-2-ylbenzamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

10 *N*-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

15 *N*-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

N-[1-(4-Aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-

20 phenylnicotinamide

2-Phenylthiazole-4-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Phenylthiophene-2-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 4-Phenylthiophene-2-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 3-Phenylpyrrole-1-carboxylic acid [1-(4-aminobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl] benzamide

4-*tert*-Butyl-*N*-[1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

25 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

4-Dimethylamino-*N*-[1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

30 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-isopropylbenzamide

4-Difluoromethoxy-*N*-[1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

10 3-Bromo-*N*-[1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

15 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

Naphthalene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Naphthalene-1-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Quinoline-6-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Benzo[*b*]thiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 Benzo[*b*]thiophene-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzothiazole-5-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Biphenyl-4-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-

5 4-yl)ethyl]amide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxy benzamide

10 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxy benzamide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-imidazol-1-ylbenzamide

15 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

20 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3]thiadiazol-5-ylbenzamide

25 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

30 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenylnicotinamide

2-Phenylthiazole-4-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Phenylthiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 5-Pyridin-3-ylthiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 2-Methyl-5-phenylfuran-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Phenylthiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 4-Pyridin-3-ylthiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 2-Thiophen-2-ylthiazole-4-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 3-Phenylpyrrole-1-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-[2-(4-*tert*-Butyl-benzylsulfanyl)-4-methyl-pentanoyl]-tetrahydrofuro[3,2-b] pyrrol-3-one

4-[2-(4-*tert*-Butyl-benzylsulfanyl)-3-(4-hydroxy-phenyl)-propionyl]-tetrahydro-

5 furo[3,2-b]pyrrol-3-one

2-Isobutyl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-4-(3-phenyl-pyrrol-1-yl)-butane-1,4-dione

2-Isobutyl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-4-(3-phenyl-pyrrolidin-1-yl)-butane-1,4-dione

10 2-(4-Hydroxybenzyl)-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-4-(3-phenyl-pyrrol-1-yl)-butane-1,4-dione

2-(4-Hydroxybenzyl)-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-4-(3-phenyl-pyrrolidin-1-yl)-butane-1,4-dione

15 4-(1,3-Dihydro-isoindol-2-yl)-2-isobutyl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-butane-1,4-dione

4-(1,3-Dihydro-isoindol-2-yl)-2-(4-hydroxybenzyl)-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-butane-1,4-dione

4-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-isobutyl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-butane-1,4-dione

20 4-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(4-hydroxybenzyl)-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-butane-1,4-dione

Further compounds of the invention include, but are not limited to, the following examples that are the (3a*S*, 7a*R*) or (3a*R*, 7a*S*) isomer of general formula (II), where
25 Z = 'O' and R¹ = 'H' and also include the equivalent analogues included in the full definition of Z and R¹

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

4-*tert*-Butyl-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-trifluoromethoxybenzamide

10 4-Dimethylamino-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-isopropylbenzamide

15 4-Difluoromethoxy-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-trifluoromethylbenzamide

20 4-Bromo-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

25 3-Bromo-*N*-[1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-vinylbenzamide

30 Naphthalene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

5 Quinoline-6-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

10 Benzo[*b*]thiophene-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

15 Benzothiazole-5-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Biphenyl-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

20 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-phenoxybenzamide

25 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-3-phenoxybenzamide

30 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-imidazol-1-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-thiophen-2-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-oxazol-5-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-

5 [1,2,3]thiadiazol-5-ylbenzamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

10 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-6-phenylnicotinamide

15 2-Phenylthiazole-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

20 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

5-Phenylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

25 5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

30 4-Phenylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

5 2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

10 3-Phenylpyrrole-1-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide

15 4-*tert*-Butyl-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-trifluoromethoxybenzamide

20 4-Dimethylamino-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide

25 4-Isopropyl-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide

4-Difluoromethoxy-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide

30 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-trifluoromethylbenzamide

4-Bromo-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl] benzamide

5 3-Bromo-*N*-[3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl] benzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-vinyl benzamide

10 Naphthalene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

Naphthalene-1-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

15 Quinoline-6-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

20 Benzo[*b*]thiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

Benzo[*b*]thiophene-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

25 Benzothiazole-5-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

Biphenyl-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

30 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-phenoxy benzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-3-phenoxy benzamide

5 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-thiophen-2-ylbenzamide

10 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-oxazol-5-ylbenzamide

15 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-[1,2,3]thiadiazol-4-ylbenzamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-pyrazol-1-ylbenzamide

20 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-5-thiophen-2-ylnicotinamide

N-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-6-phenyl nicotinamide

25 2-Phenylthiazole-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

30 2-Pyridin-3-ylthiazole-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

5-Phenylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]

5 pyridine-4-carbonyl) butyl]amide

2-Methyl-5-phenylfuran-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

10 4-Phenylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

15

2-Thiophen-2-ylthiazole-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

20 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [3-methyl-1-(3-oxohexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

3-Phenylpyrrole-1-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

25

Additional compounds of the invention include, but are not limited to, the following examples that are the (3a*S*, 6a*R*) isomer of general formula (I), where Z = 'O' and R¹ = 'H', and also include the equivalent analogues included in the full definition of Z and R¹

30

N-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

4-*tert*-Butyl-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 *N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

4-Dimethylamino-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

10 4-Isopropyl-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

15 4-Difluoromethoxy-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

N-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethylbenzamide

20 4-Bromo-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

3-Bromo-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

25 *N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-vinylbenzamide

30 Naphthalene-2-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Naphthalene-1-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 Quinoline-6-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Benzo[*b*]thiophene-3-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Benzothiazole-5-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Biphenyl-4-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 *N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-phenoxy benzamide

N-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenoxy benzamide

25 4-Imidazol-1-yl-*N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl] benzamide

N-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

30 *N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-oxazol-5-ylbenzamide

N-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-[1,2,3] thiadiazol-4-ylbenzamide

5 *N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-pyrazol-1-ylbenzamide

N-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide

10 *N*-[1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-6-phenyl nicotinamide

15 2-Phenylthiazole-4-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

2-Pyridin-3-ylthiazole-4-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 5-Phenylthiophene-2-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5-Pyridin-3-ylthiophene-2-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 2-Methyl-5-phenylfuran-3-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 4-Phenylthiophene-2-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*] pyrrol-4-yl)ethyl]amide

2-Thiophen-2-ylthiazole-4-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*] pyrrol-4-yl)ethyl]amide

2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*] pyrrol-4-yl)ethyl]amide

10 3-Phenylpyrrole-1-carboxylic acid [1-Cyclopropylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

4-*tert*-Butyl-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl] benzamide

15 *N*-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-trifluoromethoxy benzamide

4-Dimethylamino-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)

20 butyl]benzamide

4-Isopropyl-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl] benzamide

4-Difluoromethoxy-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)

25 butyl]benzamide

N-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-trifluoromethyl benzamide

30 4-Bromo-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl] benzamide

3-Bromo-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl] benzamide

N-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-vinyl benzamide

Naphthalene-2-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)

5 butyl]amide

Naphthalene-1-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)

butyl]amide

10 Quinoline-6-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)
butyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-
carbonyl) butyl]amide

15

Benzo[*b*]thiophene-3-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-
carbonyl) butyl]amide

20

Benzothiazole-5-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)
butyl]amide

Biphenyl-4-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)
butyl]amide

25

N-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-phenoxy benzamide

N-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-3-phenoxy benzamide

4-Imidazol-1-yl-*N*-[1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]

30 benzamide

1 *N*-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) benzamide] butyl]-4-thiophen-2-yl

5 *N*-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) benzamide] butyl]-4-oxazol-5-yl

10 *N*-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) benzamide] butyl]-4-[1,2,3]thiadiazol-4-yl benzamide

15 *N*-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) nicotinamide] butyl]-5-thiophen-2-yl

20 *N*-[1-(3-Oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-6-phenylnicotinamide

25 2-Phenylthiazole-4-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

30 2-Pyridin-3-ylthiazole-4-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

35 5-Phenylthiophene-2-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

40 5-Pyridin-3-ylthiophene-2-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

45 2-Methyl-5-phenylfuran-3-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

4-Phenylthiophene-2-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

4-Pyridin-3-ylthiophene-2-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-

5 carbonyl) butyl]amide

2-Thiophen-2-ylthiazole-4-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

10 2-Methyl-5-(pyrrolidine-1-sulfonyl)furan-3-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

3-Phenylpyrrole-1-carboxylic acid [1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

15 4-Methyl-*N*-(3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl)benzamide

20 4-Methoxy-*N*-(3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl)benzamide

N-(3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl)-4-morpholin-4-ylbenzamide

25 4-*tert*-Butyl-*N*-(1-(4-methoxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl)benzamide

Naphthalene-2-carboxylic acid [1-(4-methoxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 Biphenyl-4-carboxylic acid [1-(4-methoxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

4-*tert*-Butyl-N-[1-(4-hydroxymethylbenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 Naphthalene-2-carboxylic acid [1-(4-hydroxymethylbenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Biphenyl-4-carboxylic acid [1-(4-hydroxymethylbenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Furan-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Thiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Morpholine-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenylacetamide

30 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide

Furan-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

5 Furan-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

Thiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

10 Thiophene-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

Morpholine-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

15 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-2-phenyl acetamide

20 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-3-phenyl propionamide

Furan-2-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Furan-3-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Thiophene-2-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 Thiophene-3-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 *N*-[1-Cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenylacetamide

10 *N*-[1-Cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide

15 *N*-[1-Cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

20 Naphthalene-1-carboxylic acid [1-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Benzo[*b*]thiophene-2-carboxylic acid [1-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 Furan-2-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

35 Furan-3-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

40 Thiophene-2-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

45 Thiophene-3-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

Morpholine-4-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

N-[3,3-Dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-2-phenyl

5 acetamide

N-[3,3-Dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-3-phenyl
propionamide

10 Benzo[*b*]thiophene-2-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

N-[3,3-Dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]
benzamide

15 Furan-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)
ethyl]amide

20 Furan-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)
ethyl]amide

Thiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 Thiophene-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

30 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenyl
acetamide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenyl propionamide

5 Benzo[*b*]thiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

10 Furan-2-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Furan-3-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Thiophene-2-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Thiophene-3-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydro furo[3,2-*b*]pyrrol-4-yl)ethyl]amide

25 *N*-[1-Cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenylacetamide

N-[1-Cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide

30 *N*-[1-Cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl] benzamide

Naphthalene-1-carboxylic acid [1-cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

5 Benzo[*b*]thiophene-2-carboxylic acid [1-cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Furan-2-carboxylic acid [1-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10 Furan-3-carboxylic acid [1-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15 Thiophene-2-carboxylic acid [1-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Thiophene-3-carboxylic acid [1-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

20 Morpholine-4-carboxylic acid [1-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-Benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenylacetamide

25 *N*-[1-Benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide

30 Benzo[*b*]thiophene-2-carboxylic acid [1-benzylsulfanylmethyl-2-oxo-2-(3-oxohexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

N-[1-Benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide

5 Naphthalene-1-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

Furan-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

10 Furan-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

Thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

15

Thiophene-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

20 Morpholine-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]-2-phenylacetamide

25 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]-3-phenylpropionamide

Benzo[*b*]thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

30

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]benzamide

Naphthalene-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

5 4-(2-Benzylxyloxy-3-cyclohexyl-propionoyl)tetrahydrofuro[3,2-*b*]pyrrol-3-one

4-[2-(4-*tert*-Butylbenzyloxy)-4-methyl-pentanoyl]tetrahydrofuro[3,2-*b*]pyrrol-3-one

10 4-[2-(Naphthalen-1-ylmethoxy)-3-phenyl-propionyl]-tetrahydro-furo[3,2-*b*] pyrrol-3-one

15 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulfanyl)propionoyl]tetrahydrofuro[3,2-*b*]pyrrol-3-one

20 4-[3-Cyclohexyl-2-(furan-3-ylmethanesulfanyl)propionoyl]tetrahydrofuro[3,2-*b*]pyrrol-3-one

25 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulphonyl)propionoyl]tetrahydrofuro[3,2-*b*]pyrrol-3-one

Morpholine-4-carboxylic acid 1-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydro-furo[3,2-*b*]pyrrol-4-yl)-ethyl ester

30 Morpholine-4-carboxylic acid 3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl)-butyl ester

Morpholine-4-carboxylic acid 3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-b] pyrrole-4-carbonyl)-butyl ester

2-Cyclohexylmethyl-4-morpholin-4-yl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)butane-1,4-dione

5 2-Isobutyl-4-morpholin-4-yl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-butane-1,4-dione

2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)-butane-1,4-dione

4-(2-Biphenyl-3-yl-4-methylpentanoyl)tetrahydrofuro[3,2-b]pyrrol-3-one

10

Further additional compounds of the invention include, but are not limited to, the following examples that are the (3a*S*, 7a*R*) or (3a*R*, 7a*S*) isomer of general formula (II) where Z = 'O' and R¹ = 'H', and also include the equivalent analogues included in the full definition of Z and R¹

15

Furan-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide

20

Furan-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide

Thiophene-2-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide

25

Thiophene-3-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-2-phenylacetamide

5 *N*-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-3-phenylpropionamide

N-[1-(4-Hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

10 Furan-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

15 Furan-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

Thiophene-2-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

20 Thiophene-3-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

Morpholine-4-carboxylic acid [3-methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

25 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-2-phenylacetamide

30 *N*-[3-Methyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-3-phenylpropionamide

Furan-2-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

5 Furan-3-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Thiophene-2-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

10 Thiophene-3-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

15 *N*-[1-Cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-2-phenylacetamide

20 *N*-[1-Cyclohexylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-3-phenylpropionamide

N-[1-Cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

25 Naphthalene-1-carboxylic acid [1-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Benzo[*b*]thiophene-2-carboxylic acid [1-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

30 Furan-2-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl)butyl]amide

Furan-3-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

5 Thiophene-2-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

Thiophene-3-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

10 Morpholine-4-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

15 *N*-[3,3-Dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-2-phenyl acetamide

N-[3,3-Dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-3-phenyl propionamide

20 Benzo[*b*]thiophene-2-carboxylic acid [3,3-dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide

N-[3,3-Dimethyl-1-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide

25 Furan-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl) ethyl]amide

30 Furan-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl) ethyl]amide

Thiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Thiophene-3-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-

5 4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

10 *N*-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-2-phenylacetamide

N-[1-Benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-3-phenylpropionamide

15 Benzo[*b*]thiophene-2-carboxylic acid [1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

N-[1-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

20 Furan-2-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

25 Furan-3-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Thiophene-2-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

30 Thiophene-3-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Morpholine-4-carboxylic acid [1-cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

N-[1-Cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-2-

5 phenylacetamide

N-[1-Cyclopentylmethyl-2-oxo-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-3-phenylpropionamide

10 *N*-[1-Cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

Naphthalene-1-carboxylic acid [1-cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

15 Benzo[*b*]thiophene-2-carboxylic acid [1-cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

20 Furan-2-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Furan-3-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

25 Thiophene-2-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Thiophene-3-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

30 Morpholine-4-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

N-[1-Benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-2-phenylacetamide

5 *N*-[1-Benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-3-phenylpropionamide

Benzo[*b*]thiophene-2-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

10 *N*-[1-Benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide

15 Naphthalene-1-carboxylic acid [1-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide

Furan-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl methyl)ethyl]amide

20 Furan-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl methyl)ethyl]amide

Thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl methyl)ethyl]amide

25 Thiophene-3-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl methyl)ethyl]amide

30 Morpholine-4-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl methyl)ethyl]amide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl)methyl]ethyl]-2-phenylacetamide

N-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl

5 (methyl)ethyl]-3-phenylpropionamide

Benzo[*b*]thiophene-2-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

10 *N*-[2-Oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonyl methyl)ethyl]benzamide

Naphthalene-1-carboxylic acid [2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)-1-(phenylmethanesulfonylmethyl)ethyl]amide

15

Morpholine-4-carboxylic acid 1-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl ester

4-[3-Cyclohexyl-2-(furan-2-ylmethanesulfanyl)propionyl]hexahydrofuro[3,2-b]pyridin-3-one

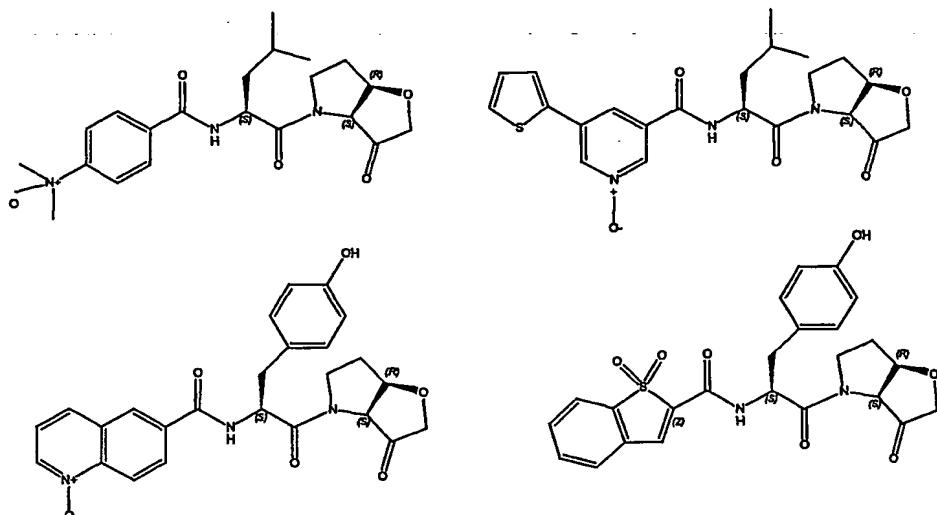
20 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulphonyl)propionyl]hexahydrofuro[3,2-b]pyridin-3-one

4-[3-Cyclohexyl-2-(furan-3-ylmethanesulfanyl)propionyl]hexahydrofuro[3,2-b]pyridin-3-one

4-[3-Cyclohexyl-2-(furan-3-ylmethanesulphonyl)propionyl]hexahydrofuro[3,2-b]pyridin-3-one

2-Cyclohexylmethyl-4-morpholin-4-yl-1-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)butane-1,4-dione

Considering all of the above examples, it is also intended to include the oxidised analogues of capping groups that contain a readily oxidised nitrogen to give the N-oxide or a readily oxidised sulphur to give the sulphone. The following structures are illustrative examples;



5

To those skilled in the practices of organic chemistry, compounds of general formulae (I) and (II) may be readily synthesised by a number of chemical strategies, 10 performed either in solution or on the solid phase (see Atherton, E. and Sheppard, R. C. In '*Solid Phase Peptide Synthesis: A Practical Approach*', Oxford University Press, Oxford, U.K. 1989, for a general review of solid phase synthesis principles). The solid phase strategy is attractive in being able to generate many thousands of analogues, typically on a 5-100mg scale, through established parallel synthesis 15 methodologies (e.g. see (a) Bastos, M.; Maeji, N. J.; Abeles, R. H. *Proc. Natl. Acad. Sci. USA*, 92, 6738-6742, 1995).

Therefore, one strategy for the synthesis of compounds of general formulae (I) and (II) comprises:-

(a) Preparation of an appropriately functionalised and protected bi-cyclic ketone building block in solution.

(b) Attachment of the building block (a) to the solid phase through a linker that is stable to the conditions of synthesis, but readily labile to cleavage at the end of a synthesis (see James, I. W., *Tetrahedron*, 55(Report N° 489), 4855-4946, 1999, for examples of the 'linker' function as applied to solid phase synthesis).

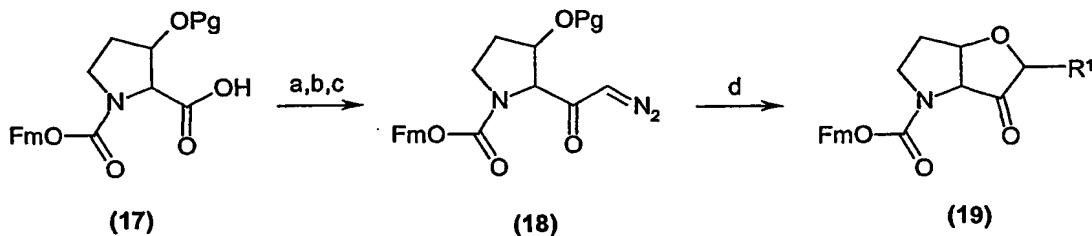
5 (c) Solid phase organic chemistry (see Brown, R. D. *J. Chem. Soc., Perkin Trans. I*, 19, 3293-3320, 1998), to construct the remainder of the molecule.

(d) Compound cleavage from the solid phase into solution.

10 (e) Cleavage work-up and compound analysis.

The first stage in a synthesis of compounds of general formulae (I) and (II) is the preparation in solution of a functionalised and protected building block. A typical scheme towards the tetrahydrofuro[3,2-*b*]pyrrol-3-one (19) is detailed in Scheme 1.

15 The following descriptions detailed in Schemes 1-13 could equally be applied using alternative scaffolds of general formulae (I) and (II).



20 Scheme 1. (a) $^3\text{BuOCOCl}$, NMM, DCM, -15°C , 10mins, under argon. (b) Diazomethane in diethyl ether, -15°C to RT over 1hr. (c) Acetic acid (d) LiCl (10eq) in 80%aq acetic acid, 5°C to RT over 1hr.

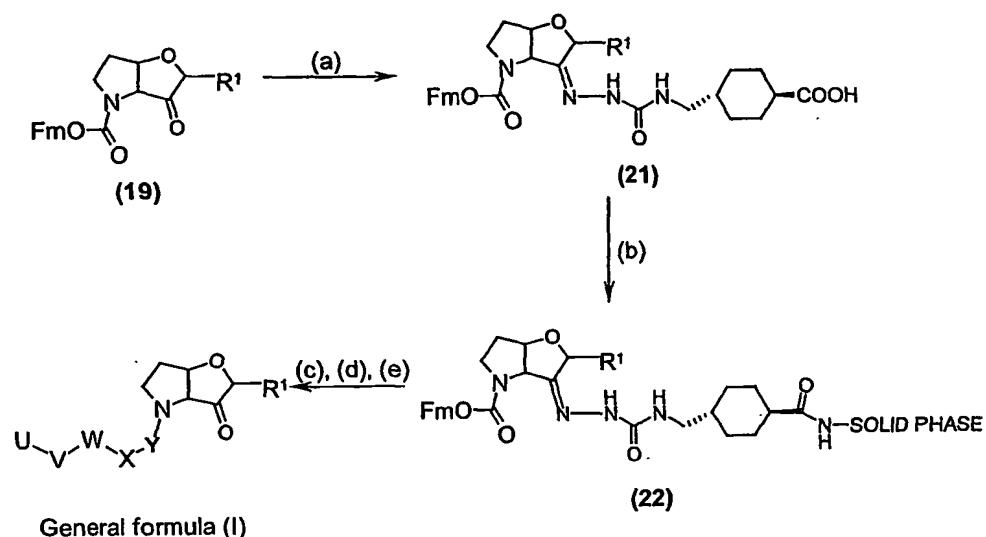
FmOC(O) denotes the well known amine protecting group 9-fluorenyl methoxycarbonyl (Fmoc, see Atherton, E. and Sheppard, R. C., 1989) and 'Pg' denotes either a free hydroxyl or an hydroxyl protecting group such as *tert*-butyl ether. In the illustrated case, condensation with diazomethane provides $R^1 = H$. Although formation of the diazoketone is clearly observed at 1hr reaction, an overall improvement in isolated yield is obtained by leaving the reaction with ethereal diazomethane for 24hr.

Considering step (a), synthesis may commence from suitably protected β -hydroxyproline (17) (or protected β -hydroxypipeolic acid), which are accessible through a variety of literature methods e.g. (a) Heffner, R. J., *et al*, *J. Am. Chem. Soc.*, 114, 10181-10189, 1992; (b) Hughes, P. Cardy, J., *J. Org. Chem.*, 54, 3260-3264, 1989, (c) Heffner, R. J., Jouille, M. M., *Tet. Lett.*, 30, 7021-7024, 1989, (d) Ewing, W. R., Jouille, M. M., *Heterocycles*, 27, 2843-2850, 1988. (e) Kolodziej, S. A., Marshall, G. R., *Int. J. Pept. Prot. Res.*, 48, 274-280, 1996, (f) Evans, D. A., Weber, A. E., *J. Am. Chem. Soc.*, 109, 7151-7157, 1987, (g) Langlois, N., Rakotondradany, F., *Tetrahedron*, 56, 2437-2448, 2000, (h) Sugisaki, C. H., *et al*, *Tet. Lett.*, 39, 3413-3416, 1998, (i) Greck, C., *et al*, *Tet. Lett.*, 37, 2031-, 1996, (j) Agami, C., *et al*, *Tet. Lett.*, 37, 4001-, 1996.

Activation of the suitably protected β -hydroxyproline (17) via isobutyl chloroformate mixed anhydride, followed by condensation with diazomethane, yields the diazomethylketone intermediates (18). Treatment of diazomethylketone intermediates (18) with lithium chloride in aqueous acetic acid provides the protected tetrahydrofuro[3,2-*b*]pyrrol-3-one (19). Introduction of simple R^1 substituents may be achieved by condensation of activated (17) with alternatives to diazomethane such as diazoethane ($R^1 = CH_3$), or 1-phenyloxydiazoethane ($R^1 = CH_2OPh$).

The protected building blocks (synthesis exemplified by the tetrahydrofuro[3,2-*b*]pyrrol-3-one (19)) detailed in Scheme 1 may be utilised in a solid phase synthesis of inhibitor molecules (steps (b) to (e)). Step (b), the solid phase linkage of an aldehyde or ketone, has previously been described by a variety of methods (e.g. see (a) James, I. W., 1999, (b) Lee, A., Huang, L., Ellman, J. A., *J. Am. Chem. Soc.*, 121(43), 9907-9914, 1999, (c) Murphy, A. M., *et al*, *J. Am. Chem. Soc.*, 114, 3156-3157, 1992). A suitable method amenable to the reversible linkage of an alkyl ketone functionality such as (19) is through a combination of the previously described chemistries. The semicarbazide, 4-[[[hydrazinocarbonyl]amino]methyl]cyclohexane carboxylic acid. trifluoroacetate (20) (Murphy, A. M., *et al*, *J. Am. Chem. Soc.*, 114, 3156-3157,

1992), may be utilised as illustrated in Scheme 2, exemplified by linkage of the tetrahydrofuro[3,2-*b*]pyrrol-3-one (19).



Scheme 2. (a) (19) in 90% EtOH / H₂O / 1.5eq NaOAc / 4-[[[hydrazinocarbonyl]amino]methyl]-cyclohexane carboxylic acid.trifluoroacetate (20), 2hr reflux. (b) 3eq construct (21) / 3eq HBTU / 3eq HOBr / 6eq NMM, NH₂-SOLID PHASE, DMF, RT, o/n. (c) 20% piperidine / DMF, 30mins. (d) Range of chemistries to introduce U-V-W-X-Y (e) TFA / H₂O (95:5, v/v), RT, 2hr

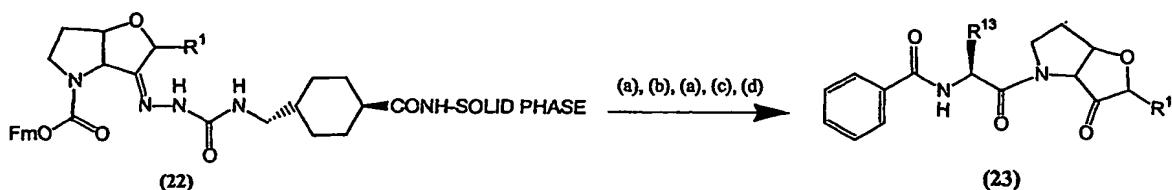
10

Construct (21) is prepared through reaction of the linker molecule (20) and the tetrahydrofuro[3,2-*b*]pyrrol-3-one (19) by reflux in aqueous ethanol / sodium acetate. Standard solid phase techniques (e.g. see Atherton, E. and Sheppard, R. C., 1989) are used to anchor the construct to an amino-functionalised solid phase through the free carboxylic acid functionality of (21), providing the loaded construct (22).

15

Loaded construct (22) may be reacted with a wide range of carboxylic acids available commercially or in the literature, to introduce the left-hand portion 'U-V-W-X-Y' in general formula (I). In the simplest example, the entire left hand portion of an inhibitor of general formula (I) comprises a capped aminoacid (Scheme 3), providing for example analogues of general formula (I) where R¹² = 'H', (X)₀ = '—', (W)_n = 'NH', R¹⁶ = 'H', n = 1, (V)_m = 'CO', m = 1 and U = aryl

20



General formula (I) where

$$R^{12} = H$$

$$\infty_1 = 1$$

$(W)_n = 'NH'$, $n = 1$

(M_m = 'CO', m = 1)

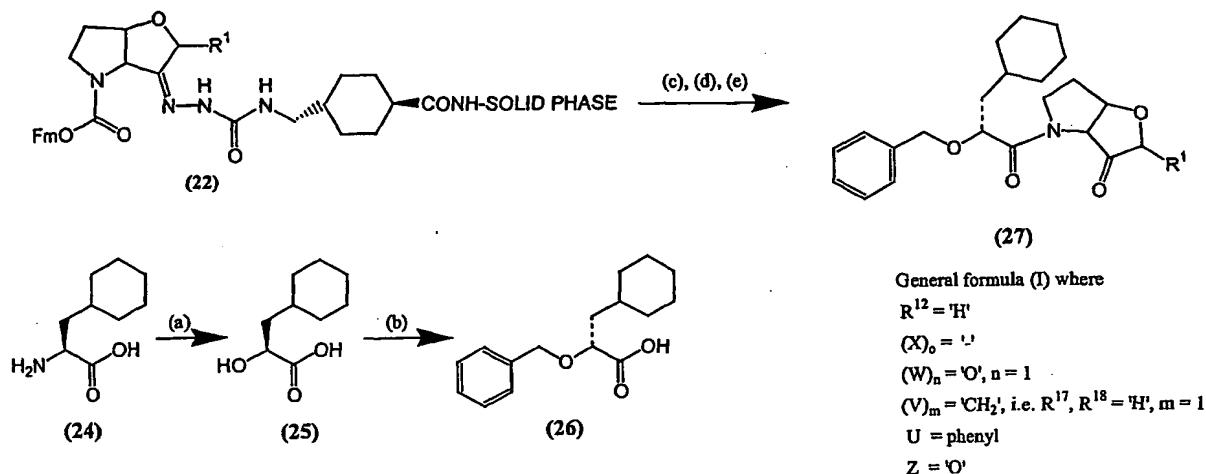
U = phenyl

Z = '0'

Scheme 3. (a) 20% piperidine / DMF, 30mins (b) 20eq Fmoc-aminoacid / 20eq HBTU / 20eq HOEt / 40eq NMM, DMF, o/n (c) 5eq carboxylic acid / 5eq HBTU / 5eq HOEt / 10eq NMM, DMF, RT, o/n (d) TFA / H₂O (95:5, v/v), RT, 2hr.

5 Alternatively, carboxylic acids can be prepared in solution by traditional organic chemistry methods and coupled to construct (22) on the solid phase (Schemes 4-8). For example (Scheme 4), treatment in solution of an amino acid, exemplified by (24) with sodium nitrite / H_2SO_4 , provides the α -hydroxyacid, exemplified by (25) (Degerbeck, F. et al, *J. Chem. Soc, Perkin Trans. 1*, 11-14, 1993). Treatment of α -hydroxyacid, (25) with sodium hydride in a dimethylformamide / dichloromethane mixture followed by addition of benzyl bromide, provides 2RS-benzyloxy-3-cyclohexylpropionic acid (26). Coupling of (26) to the solid phase construct (22) followed by cleavage, provides (27), an example of general formula (I) where $\text{R}^{12} = \text{'H}'$, $(\text{X})_0 = \text{'-}'$, $(\text{W})_n = \text{'O}'$, $n = 1$, $(\text{V})_m = \text{'CH}_2\text{'}$, i.e. $\text{R}^{17}, \text{R}^{18} = \text{'H}'$, $m = 1$ and $\text{U} =$ phenyl. To those skilled in the practices of organic synthesis, a wide variety of aminoacids such as (24) may be converted to the corresponding α -hydroxyacid such as (25) following the general conditions detailed. Additionally, benzylbromide may be replaced by any reasonable $\text{Ar}-\text{CR}^{17}\text{R}^{18}$ -halide, providing many variations of carboxylic acid (26) following the general conditions detailed. In certain instances, it may be advantageous to temporarily protect the carboxylic acid as the methyl ester (for example compound (32), Scheme 6) prior to reaction with the alkylhalide. The ester intermediate is then simply hydrolysed to acid (26). Analogues of (27), exploring a wide range of $(\text{V})_m$ and U in general formula (I) may be prepared through the general conditions detailed in Scheme 4. Since the final synthetic step involves a trifluoroacetic acid (TFA) mediated cleavage of the solid phase bound compound,

analogues where the substituted ether is labile to TFA may be prepared in solution by an alternative route (see Scheme 11).

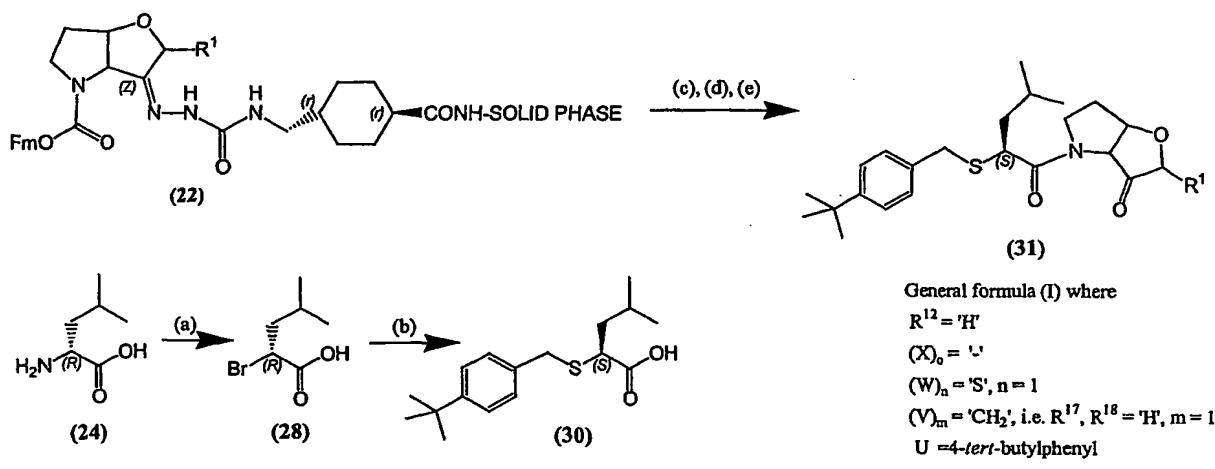


5 Scheme 4. (a) $\text{NaNO}_2 / \text{H}_2\text{SO}_4$, $0^\circ\text{C} \rightarrow \text{RT}$, 2hr (b) 2.3eq NaH , 1:1 DMF / DCM, 1.4eq benzylbromide, o/n (c) 20% piperidine / DMF, 30mins. (d) 10eq (26) / 10eq HBTU / 10eq HOEt / 20eq NMM, DMF, RT, o/n (e) TFA / H_2O (95:5, v/v), RT, 2hr.

10 Alternatively, coupling of construct (22) (following removal of Fmoc) with the α -hydroxyacid (25), provides a versatile solid phase bound intermediate 'Y' substituent in general formula (I) that may be reacted with many reagents. For example, the α -hydroxyl can be reacted under Mitsunobu conditions (Hughes, D. L. *Org. React. (N.Y.)*, 42, 335-656, 1992) to give ethers (i.e. $X = '-'$, $W = 'O'$, in general formula (I)) (see Grabowska, U. *et al*, *J. Comb. Chem.*, 2(5), 475-490, 2000, for an example of Mitsunobu reaction on the solid phase). Alternatively, the α -hydroxyl can be reacted with a carbamoyl chloride to give a carbamate (i.e. $X = '-'$, $W = 'O'$, $V = 'NHC(O)'$, in general formula (I)).

20 Alternatively, (Scheme 5), treatment in solution of an amino acid, exemplified by (24) with sodium nitrite / H_2SO_4 / potassium bromide provides the α -bromoacid, exemplified by (28) (Souers, A. J. *et al*, *Synthesis*, 4, 583-585, 1999) with retention of configuration. Treatment of α -bromoacid (28) with an alkylthiol exemplified by 4-*tert*-butylphenylmethanethiol (29) in dimethylformamide / triethylamine, provides

2S-(4-*tert*-butylbenzylsulfonyl)-4-methylpropionic acid (30), with inversion of configuration. Coupling of (30) to the solid phase construct (22) followed by cleavage, provides (31), an example of general formula (I) where R¹² = 'H', (X)₀ = '—', (W)_n = 'S', n = 1, (V)_m = 'CH₂', i.e. R¹⁷, R¹⁸ = 'H', m = 1 and U = 4-*tert*-butylphenyl. To those skilled in the practices of organic synthesis, a wide variety of aminoacids such as (24) may be converted to the corresponding α -bromoacid such as (28) following the general conditions detailed. Additionally, starting with the S-isomer of (24) gives the S-bromoacid analogue of (28) and R-thioether analogue of (30). Additionally, (4-*tert*-butylphenyl)methanethiol (29) may be replaced by any reasonable Ar-CR¹⁷R¹⁸-SH, providing many variations of carboxylic acid (30) following the general conditions detailed. Thus analogues of (31) exploring a wide range of (V)_m and U in general formula (I) may be prepared through the general conditions detailed in Scheme 5.



15 Scheme 5. (a)NaNO₂ / H₂SO₄, KBr 0°C → RT, 2hr (b) Alkylthiol (29) / DMF / NEt₃, o/n (c) 20% piperidine / DMF, 30mins. (d) 10eq (30) / 10eq HBTU / 10eq HOEt / 20eq NMM, DMF, RT, o/n (e) TFA / H₂O (95:5, v/v), RT, 2hr.

20 Alternatively, coupling of construct (22) (following removal of Fmoc) with an α -bromoacid e.g. (28), provides a versatile intermediate 'Y' substituent in general formula (I) that may be reacted with many reagents. For example, the α -bromide can be displaced with nucleophiles e.g. alcohols, thiols, carbanions etc, to give ethers (i.e. X = '—', W = 'O', in general formula (I)), thioethers (i.e. X = '—', W = 'S', in general

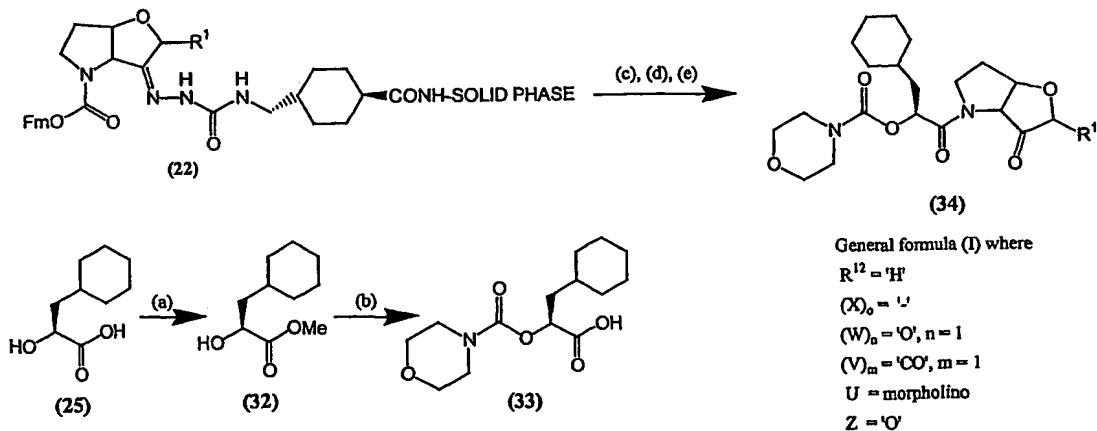
formula (I)). The thioethers may optionally be oxidised to the sulphone (see Scheme 9, i.e. X = ‘-‘, W = ‘SO₂’, in general formula (I)) (see Grabowska, U. *et al*, *J. Comb. Chem.*, 2(5), 475-490, 2000, for an example of bromide displacement and thioether oxidation on the solid phase).

5

Alternatively, (Scheme 6), treatment of an α -hydroxyacid, exemplified by (25) with trimethylsilylchloride and methanol provides the methyl ester (32). Activation of the free hydroxyl to the chloroformate with phosgene in dichloromethane followed by addition of morpholine, then hydrolysis, provides morpholine-4-carboxylic acid-1S-carboxy-2-cyclohexyl ethyl ester (33). Coupling of (33) to the solid phase construct (22) followed by cleavage, provides (34), an example of general formula (I) where R¹² = ‘H’, (X)₀ = ‘-‘, (W)_n = ‘O’, n = 1, (V)_m = ‘CO’ and U = morpholino. To those skilled in the practices of organic synthesis, a wide variety of α -hydroxyacid esters such as (32) could be converted to the activated chloroformate following the general conditions detailed. Additionally, morpholine may be replaced by any reasonable amine, providing many variations of carboxylic acid (33) following the general conditions detailed. Thus analogues of (34) exploring a wide range of (V)_m and U in general formula (I) may be prepared through the general conditions detailed in Scheme 6.

15

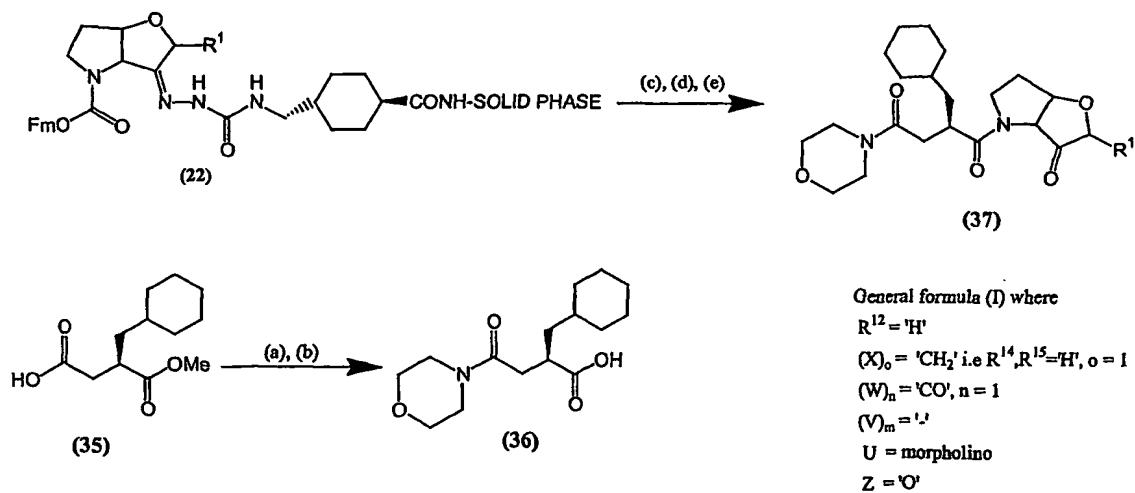
20



Scheme 6. (a) Me₃SiCl, MeOH, RT, o/n.. (b) i. COCl₂ / DCM / o/n, ii. Morpholine / DCM 0°C, 2hr, iii. LiOH in H₂O / dioxan, 0°C. (c) 20% piperidine / DMF, 30mins. (d) 10eq (33) / 10eq HBTU / 10eq HOEt / 20eq NMM, DMF, RT, o/n (e) TFA / H₂O (95:5, v/v), RT, 2hr.

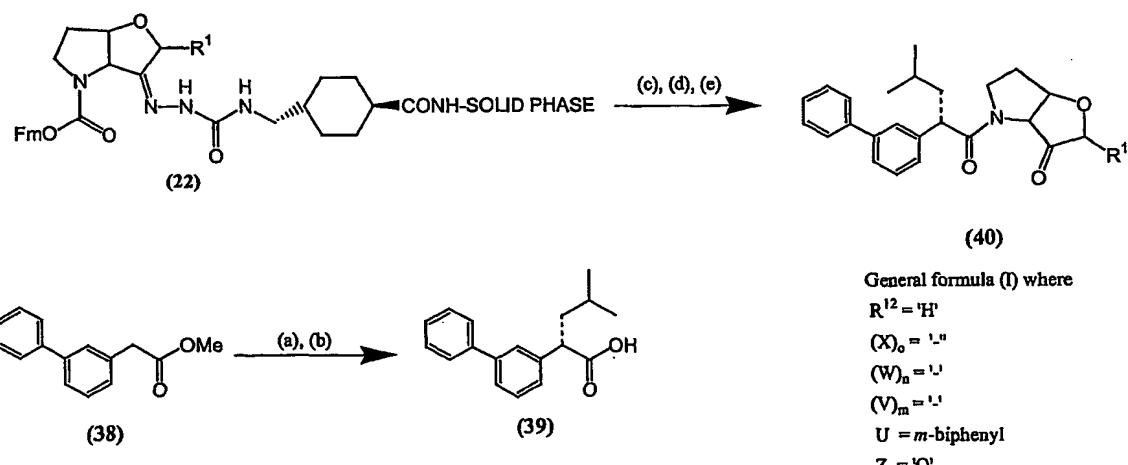
Alternatively, (Scheme 7), a wide range of alkylsuccinate esters exemplified by 2*R*-cyclohexylmethylsuccinic acid 1-methyl ester (35) are commercially available or readily prepared by known methods (see (a) Azam *et al*, *J. Chem. Soc. Perkin Trans. 1*, 621-, 1996; (b) Evans *et al*, *J. Chem. Soc. Perkin Trans. 1*, 103, 2127, 1981; (c) Oikawa *et al*, *Tet. Lett.*, 37, 6169, 1996). Carboxyl activation of alkylsuccinate ester (35) followed by addition of morpholine in dimethylformamide and subsequent ester hydrolysis, provides 2*R*-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (36). Coupling of (36) to the solid phase construct (22) followed by cleavage, provides (37), an example of general formula (I) where $R^{12} = 'H'$, $(X)_o = 'CH_2'$ i.e. $R^{14}, R^{15} = 'H'$, $o = 1$, $(W)_n = 'CO'$, $n = 1$, $(V)_m = '-'$ and $U = \text{morpholino}$. To those skilled in the practices of organic synthesis, a wide variety of alkylsuccinate esters such as (35) may be prepared and converted to the corresponding substituted alkylsuccinate acid such as (36) following the general conditions detailed. Additionally, morpholine may be replaced by any reasonable amine, providing many variations of carboxylic acid (36) following the general conditions detailed. Thus analogues of (37) exploring a wide range of $(X)_o$, $(V)_m$ and U in general formula (I) may be prepared through the general conditions detailed in Scheme 7.

20



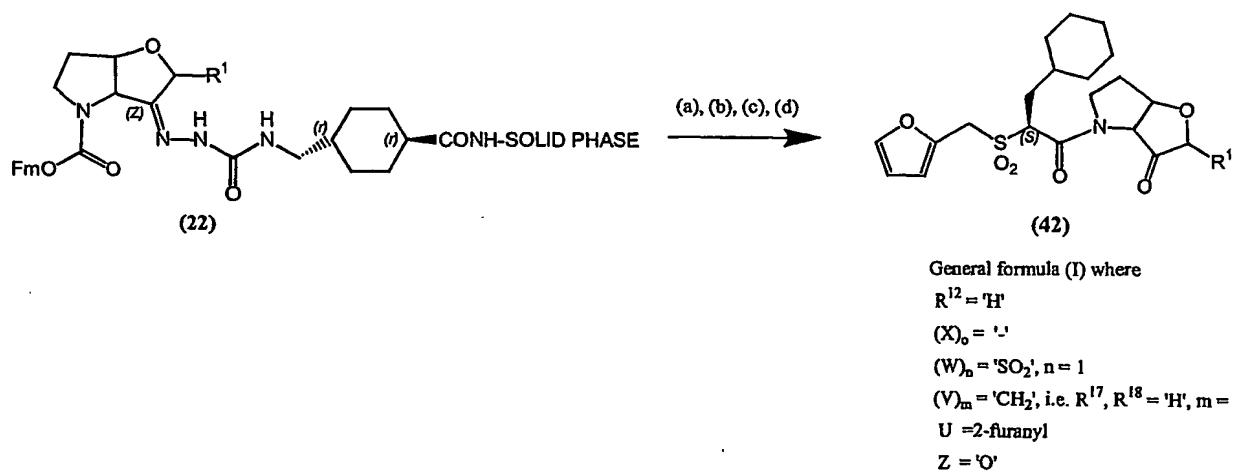
Scheme 7. (a) i. EDC / 1-hydroxybenzotriazole / DMF, 0°C, 30mins. ii. Morpholine, RT, o/n (b) LiOH in H₂O / dioxan, 0°C (c) 20% piperidine / DMF, 30mins. (d) 10eq (36) / 10eq HBTU / 10eq HOBt / 20eq NMM, DMF, RT, o/n (e) TFA / H₂O (95:5, v/v), RT, 2hr.

5 Alternatively, (Scheme 8), a wide range of biarylalkylacetic acids, exemplified by 2RS-biphenyl-3-yl-4-methylpentanoic acid (39) are readily available by known methods (see (a) DesJarlais, R. L. *et al*, *J. Am. Chem. Soc*, **120**, 9114-9115, 1998; (b) Oballa, R. M. *et al*, WO 0149288). Coupling of biarylalkylacetic acid (39) to the solid phase construct (22) followed by cleavage, provides (40), an example of 10 general formula (I) where R¹² = 'H', (X)_o = '—', (W)_o = '—', (V)_m = '—' and U = *m*-biphenyl. To those skilled in the practices of organic synthesis, a wide variety of 15 biarylalkylacetic acids such as (39) may be prepared by alkylation of the α -anion of the free acid analogue of (38), which in turn is prepared by Suzuki coupling of phenylboronic acid and 3-bromophenylacetic acid methyl ester. Phenylboronic acid may be replaced by a wide range of arylboronic acids in the Suzuki coupling, 20 providing many variations of carboxylic acid (39) following the general conditions detailed. Thus analogues of (40) exploring a wide range of group 'U' in general formula (I) may be prepared through the general conditions detailed in Scheme 8.



Scheme 8. (a) LiOH in H₂O / dioxan, 0°C (b) i. LDA, THF, 2-methylpropenylbromide. ii. Pd/C, EtOH, H₂ (c) 20% piperidine / DMF, 30mins. (d) 10eq (39) / 10eq HBTU / 10eq HOBt / 20eq NMM, DMF, RT, o/n (e) TFA / H₂O (95:5, v/v), RT, 2hr.

Many other possibilities for solid phase organic chemistry (e.g. see Brown, R. D: *J. Chem. Soc., Perkin Trans. I*, **19**, 3293-3320, 1998, for a review of recent SPOC publications) can be used to derivatise construct (22) towards compounds of general formula (I) (and similarly, through the appropriate loaded derivative, compounds of general formula (II)). For example, the left-hand portion 'U-V-W-X-Y' in general formulae (I) can be partially constructed in solution, coupled to construct (22) and further modified on the solid phase. For example (Scheme 9), a simple extension of Scheme 5 is through the oxidation of the intermediate solid phase bound species, with *m*-chloroperbenzoic acid in dichloromethane prior to cleavage, to give the sulphone analogue (42). Commencing from a variation of carboxylic acid (30), 3-cyclohexyl-2S-(furan-2-ylmethylsulfanyl)propionic acid (41), sulphone (42) is prepared, an example of general formula (I) where R^{12} = 'H', $(X)_0$ = '·', $(W)_n$ = 'SO₂', n = 1, $(V)_m$ = 'CH₂', i.e. R^{17} , R^{18} = 'H', m = 1 and U = 2-furanyl. As described in Scheme 5, many variations of carboxylic acid (30) may be prepared following the general conditions detailed e.g. (41). Thus analogues of (42) exploring a wide range of $(V)_m$ and U in general formula (I) may be prepared through the general conditions detailed in Schemes 5 and 9.



Scheme 9. (a) 20% piperidine / DMF, 30mins. (b) 5eq (41) / 5eq HBTU / 5eq HOBr / 10eq NMM, DMF, RT, o/n (c) 5eq *m*-chloroperbenzoic acid / DCM, RT, 5hr. (d) TFA / H₂O (95:5, v/v), RT, 2hr.

Compounds of general formulae (I) and (II) are finally released from the solid phase by treatment with trifluoroacetic acid / water, followed by evaporation, lyophilis and standard analytical characterisation.

5 A second strategy for the synthesis of compounds of general formulae (I) and (II) comprises:-

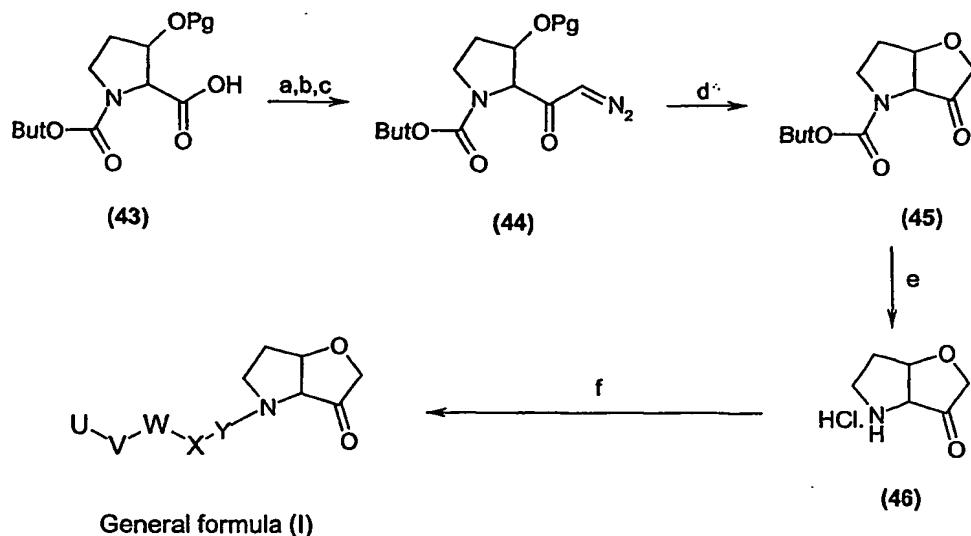
(a) Preparation of an appropriately functionalised and protected tetrahydrofuro[3,2-*b*]pyrrol-3-one, tetrahydrothieno[3,2-*b*]pyrrol-3-one, 10 hexahydropyrrolo[3,2-*b*] pyrrol-3-one, hexahydrocyclopenta[*b*]pyrrol-6-one, tetrahydrofuro[3,2-*c*]pyrazol-6-one, tetrahydrothieno[3,2-*c*]pyrazol-6-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one, hexahydrocyclopentapyrazol-6-one, hexahydrofuro[3,2-*b*]pyridin-3-one, hexahydrothieno[3,2-*b*]pyridin-3-one, octahydropyrrolo[3,2-*b*] pyridin-3-one, octahydrocyclopenta[*b*]pyridin-7-one, 15 hexahydrofuro[3,2-*c*]pyridazin-7-one, hexahydrothieno[3,2-*c*]pyridazin-7-one, octahydropyrrolo[3,2-*c*]pyridazin-7-one or octahydrocyclopenta[*c*]pyridazin-7-one building block in solution.

Preferred protecting groups for solution phase chemistry are the $\text{N}\alpha$ -*tert*-butoxycarbonyl group and the $\text{N}\alpha$ -benzyloxycarbonyl group.

20

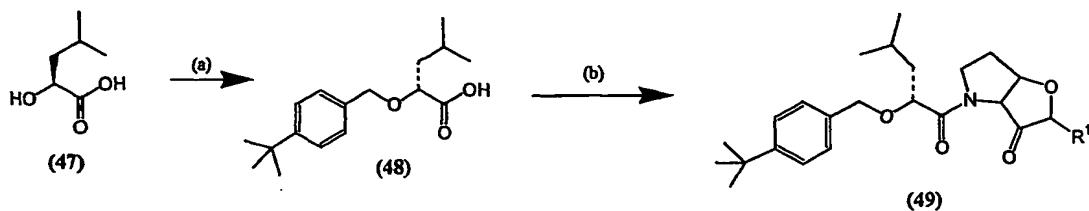
(b) Standard organic chemistry methods for the conversion of building block (a) towards compounds of general formulae (I) and (II).

In the simplest example, the entire left hand portion of an inhibitor of general 25 formulae (I) and (II) can be prepared in solution by traditional organic chemistry methods and coupled to building block (a) (see Scheme 10 exemplified by preparation and use of the 3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid *tert*-butyl ester (45)).



Scheme 10. (a) $^1\text{BuOCOCl}$, NMM, DCM, -15°C , 10mins, under argon. (b) Diazomethane in diethyl ether, -15°C to RT over 24hr. (c) Acetic acid (d) LiCl (10eq) in 80%aq acetic acid, 5°C to RT over 1hr. (e) 4M HCl in dioxan, 0°C , 2hrs. (f) Pre-prepared U-V-W-X-Y-COOH / activation e.g. HATU / HOAt / NMM, DMF, RT, o/n.

The general strategy detailed in Scheme 10 is particularly useful when the compound of general formula (I) contains a substituent that is labile to trifluoroacetic acid, this being the final reagent used in each of the solid phase Schemes 4-9. For example (Scheme 11), treatment in solution of α -hydroxyacid (47) with sodium hydride in a dimethylformamide / dichloromethane mixture followed by addition of 4-*tert*-butylbenzyl bromide, provides 2*RS*-(4-*tert*-butylbenzyloxy)-4-methylpentanoic acid (48). Coupling of (48) to hydrochloride salt (46), provides (49), an example of general formula (I) where $\text{R}^{12} = \text{'H'}$, $(\text{X})_0 = \text{'-'}$, $(\text{W})_n = \text{'O'}$, $n = 1$, $(\text{V})_m = \text{'CH}_2\text{'}$, i.e. $\text{R}^{17}, \text{R}^{18} = \text{'H'}$, $m = 1$ and $\text{U} = 4$ -*tert*-butylphenyl. To those skilled in the practices of organic synthesis, 4-*tert*-butylbenzyl bromide may be replaced by any reasonable $\text{Ar}-\text{CR}^{17}\text{R}^{18}$ -halide, providing many variations of carboxylic acid (48) under the conditions shown. Thus analogues of (49) exploring a wide range of $(\text{V})_m$ and U in general formula (I) may be prepared through the conditions detailed in Scheme 11.



General formula (I) where
 $R^{12} = 'H'$
 $(X)_o = 'L'$
 $(W)_o = 'O', n = 1$
 $(V)_m = 'CH_2', i.e. R^{17}, R^{18} = 'H', m = 1$
 $U = 4\text{-}tert\text{-butylphenyl}$
 $Z = 'O'$

Scheme 11. (a) 2.2eq NaH, 1:1 DMF / DCM, 1.25eq 4-*tert*-benzylbromide, 2hr (b) 1eq (48), 1eq $^3\text{BuOCOCl}$, 2eq NMM, DCM, -15°C, 1hr, under nitrogen, then 1eq, (46), RT, o/n.

5 A third strategy for the synthesis of compounds of general formulae (I) and (II) where the addition of U-V-W-X-Y to the protected building block involves multistep organic reactions comprises:-

10 (a) Preparation of an appropriately functionalised and protected tetrahydrofuro[3,2-*b*]pyrrol-3-one, tetrahydrothieno[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydrocyclopenta[*b*]pyrrol-6-one, tetrahydrofuro[3,2-*c*]pyrazol-6-one, tetrahydrothieno[3,2-*c*]pyrazol-6-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one, hexahydrocyclopentapyrazol-6-one, hexahydrofuro[3,2-*b*]pyridin-3-one, hexahydrothieno[3,2-*b*]pyridin-3-one, 15 octahydropyrrolo[3,2-*b*]pyridin-3-one, octahydrocyclopenta[*b*]pyridin-7-one, hexahydrofuro[3,2-*c*]pyridazin-7-one, hexahydrothieno[3,2-*c*]pyridazin-7-one, octahydropyrrolo[3,2-*c*]pyridazin-7-one or octahydrocyclopenta[*c*]pyridazin-7-one building block in solution.

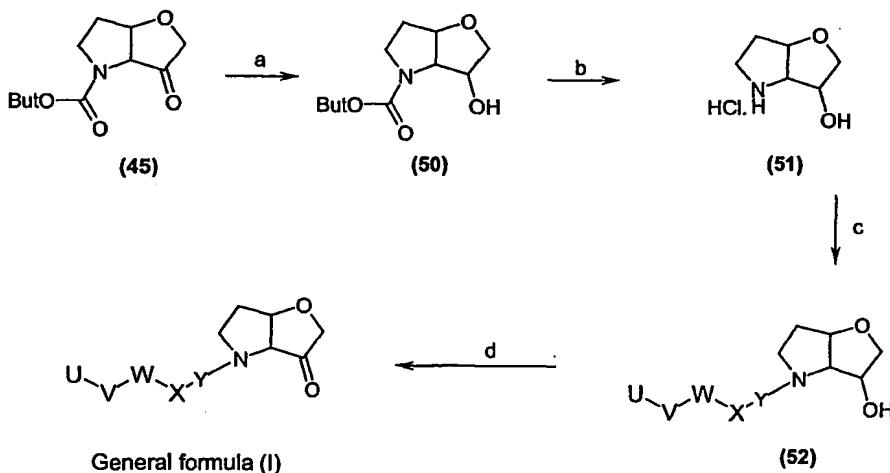
15 Preferred protecting groups for solution phase chemistry are the $\text{Na}\text{-}tert$ -butoxycarbonyl group and the $\text{Na}\text{-}benzyloxycarbonyl$ group.

(b) Protection of the ketone functionality of the tetrahydrofuro[3,2-*b*]pyrrol-3-one, tetrahydrothieno[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydrocyclopenta[*b*]pyrrol-6-one, tetrahydrofuro[3,2-*c*]pyrazol-6-

one, tetrahydrothieno[3,2-*c*]pyrazol-6-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one, hexahydrocyclopentapyrazol-6-one, hexahydrofuro[3,2-*b*]pyridin-3-one, hexahydrothieno[3,2-*b*]pyridin-3-one, octahydropyrrolo[3,2-*b*]pyridin-3-one, octahydrocyclopenta[*b*]pyridin-7-one, hexahydrofuro[3,2-*c*]pyridazin-7-one, hexahydrothieno[3,2-*c*]pyridazin-7-one, octahydropyrrolo[3,2-*c*]pyridazin-7-one or octahydrocyclopenta[*c*]pyridazin-7-one building block 5 e.g. as a dimethylacetal. Alternatively, the ketone may be reduced to the achiral secondary alcohols and re-oxidised as the final synthetic step.

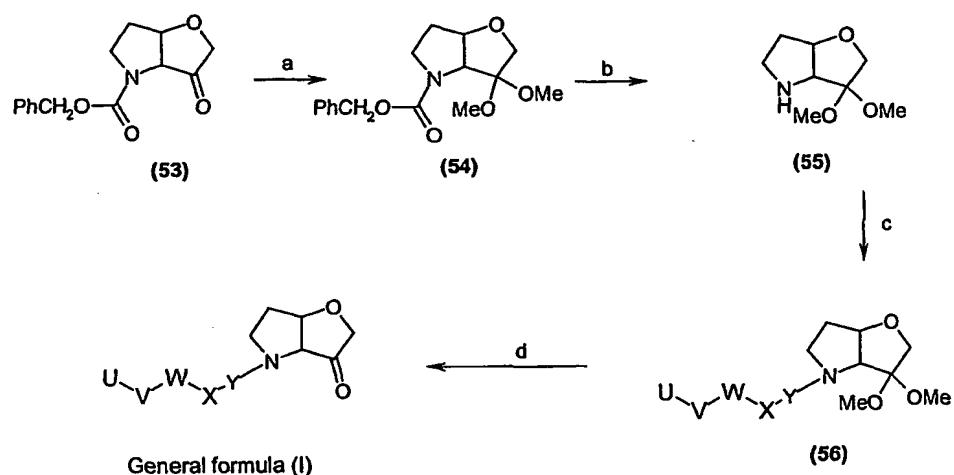
10 (c) Standard organic chemistry methods for the conversion of building block (b) towards compounds of general formulae (I) and (II).

15 (d) Intermediates may be prepared in solution, followed by coupling to building block (b) and further derivitisation towards compounds of general formulae (I) and (II) (see Scheme 12 exemplified by preparation and use of the 3-hydroxyhexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid tert-butyl ester (50)).



20 Scheme 12. (a) Reduction, e.g. NaBH_4 (b) 4M HCl in dioxan, 0°C , 2hrs. (c) Stepwise reaction with intermediates of Y, then X, then W etc., to stepwise construct compounds (52). (d) Oxidation, e.g. Dess-Martin periodane, CH_2Cl_2 .

Alternatively, depending upon the types of chemistry used to construct the left hand side U-V-W-X-Y of compounds of general formula (I) and (II), the ketone may require protection e.g. as the dimethyl acetal. Such a method is detailed and exemplified in Scheme 13 by the preparation and use of 3,3-dimethoxyhexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid benzyl ester (54).



Scheme 13. (a) Triethylorthoformate / pTSA / MeOH. (b) H₂, Pd-C. (c) Stepwise reaction with intermediates of Y, then X, then W etc., to stepwise construct compounds (56). (d) Trifluoroacetic acid / CH₂Cl₂ / H₂O.

The invention extends to novel intermediates as described above, and to processes for preparing compounds of general formulae (I) or (II) from each of their immediate precursors. In turn, processes for preparing intermediates from their immediate precursors also form part of the invention.

Compounds of general formulae (I) and (II) are useful both as laboratory tools and as therapeutic agents. In the laboratory certain compounds of the invention are useful in establishing whether a known or newly discovered cysteine protease contributes a critical or at least significant biochemical function during the establishment or progression of a disease state, a process commonly referred to as 'target validation'.

According to a second aspect of the invention, there is provided a method of validating a known or putative cysteine protease inhibitor as a therapeutic target, the method comprising:

- 5 (a) assessing the *in vitro* binding of a compound as described above to an isolated known or putative cysteine protease, providing a measure of potency; and optionally, one or more of the steps of:
- 10 (b) assessing the binding of the compound to closely related homologous proteases of the target and general house-keeping proteases (e.g. trypsin) to provides a measure of selectivity;
- 15 (c) monitoring a cell-based functional marker of a particular cysteine protease activity, in the presence of the compound; and
- (d) monitoring an animal model-based functional marker of a particular cysteine protease activity in the presence of the compound.

The invention therefore provides a method of validating a known or putative cysteine protease inhibitor as a therapeutic target. Differing approaches and levels of complexity are appropriate to the effective inhibition and 'validation' of a particular target. In the first instance, the method comprises assessing the *in vitro* binding of a compound of general formulae (I) or (II) to an isolated known or putative cysteine protease, providing a measure of 'potency'. An additional assessment of the binding of a compound of general formulae (I) or (II) to closely related homologous proteases of the target and general house-keeping proteases (e.g. trypsin) provides a measure of 'selectivity'. A second level of complexity may be assessed by monitoring a cell-based functional marker of a particular cysteine protease activity, in the presence of a compound of general formulae (I) or (II). For example, a 'human osteoclast resorption assay' has been utilised as a cell-based secondary *in vitro* testing system for monitoring the activity of cathepsin K and the biochemical effect of protease inhibitors (e.g. see WO-A-9850533). An 'MHC-II processing – T-cell

activation assay' has been utilised as a cell-based secondary *in vitro* testing system for monitoring the activity of cathepsin S and the biochemical effect of protease inhibitors (Shi, G-P., *et al, Immunity*, 10, 197-206, 1999). When investigating viral or bacterial infections such a marker could simply be a functional assessment of viral (e.g. count of mRNA copies) or bacterial loading and assessing the biochemical effect of protease inhibitors. A third level of complexity may be assessed by monitoring an animal model-based functional marker of a particular cysteine protease activity, in the presence of a compound of general formulae (I) or (II). For example, murine models of *Leishmania* infection, *P. vinckei* infection, malaria (inhibition of falcipain) and *T. cruzi* infection (cruzipain), indicate that inhibition of cysteine proteases that play a key role in pathogen propagation is effective in arresting disease symptoms, 'validating' said targets.

The invention therefore extends to the use of a compound of general formulae (I) or (II) in the validation of a known or putative cysteine protease inhibitor as a therapeutic target.

Compounds of general formulae (I) and (II) are useful for the *in vivo* treatment or prevention of diseases in which participation of a cysteine protease is implicated.

According to a third aspect of the invention, there is provided a compound of general formulae (I) or (II) for use in medicine, especially for preventing or treating diseases in which the disease pathology may be modified by inhibiting a cysteine protease.

According to a fourth aspect of the invention, there is provided the use of a compound of general formulae (I) or (II) in the preparation of a medicament for preventing or treating diseases in which the disease pathology may be modified by inhibiting a cysteine protease.

Certain cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, e.g. in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in

pathological conditions leading to disease. Thus, cysteine proteases have been implicated in various disease states, including but not limited to, infections by *Pneumocystis carinii*, *Trypanosoma cruzi*, *Trypanosoma brucei brucei* and *Crithidia fusiculata*; as well as in osteoporosis, autoimmunity, schistosomiasis, malaria, 5 tumour metastasis, metachromatic leukodystrophy, muscular dystrophy, amyotrophy, and the like. See WO-A-9404172 and EP-A-0603873 and references cited in both of them. Additionally, a secreted bacterial cysteine protease from *S. Aureus* called staphylopain has been implicated as a bacterial virulence factor (Potempa, J., *et al. J. Biol. Chem.*, 262(6), 2664-2667, 1998).

10

The invention is useful in the prevention and/or treatment of each of the disease states mentioned or implied above. The present invention also is useful in a methods of treatment or prevention of diseases caused by pathological levels of cysteine proteases, particularly cysteine proteases of the papain superfamily, which methods 15 comprise administering to an animal, particularly a mammal, most particularly a human, in need thereof a compound of the present invention. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by *Pneumocystis carinii*, *Trypanosoma cruzi*, *Trypanosoma brucei*, *Leishmania mexicana*, *Clostridium histolyticum*, *Staphylococcus aureus*, foot-and-mouth disease virus and *Crithidia fusiculata*; as well as in 20 osteoporosis, autoimmunity, schistosomiasis, malaria, tumour metastasis, metachromatic leukodystrophy, muscular dystrophy and amyotrophy.

25 Inhibitors of cruzipain, particularly cruzipain-specific compounds, are useful for the treatment of Chagas' disease.

In accordance with this invention, an effective amount of a compound of general formulae (I) or (II) may be administered to inhibit the protease implicated with a particular condition or disease. Of course, this dosage amount will further be 30 modified according to the type of administration of the compound. For example, to achieve an "effective amount" for acute therapy, parenteral administration of a compound of general formulae (I) or (II) is preferred. An intravenous infusion of the

compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of 5 drug in the plasma at a concentration effective to inhibit a cysteine protease. The compounds may be administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by 10 comparing the blood level of the agent to the concentration required to have a therapeutic effect. Prodrugs of compounds of the present invention may be prepared by any suitable method. For those compounds in which the prodrug moiety is a ketone functionality, specifically ketals and/or hemiacetals, the conversion may be effected in accordance with conventional methods.

15

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose 20 of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention. The compounds 25 of this invention, which may have good bioavailability, may be tested in one of several biological assays to determine the concentration of a compound which is required to have a given pharmacological effect.

According to a fifth aspect of the invention, there is provided a pharmaceutical or 30 veterinary composition comprising one or more compounds of general formulae (I) or (II) and a pharmaceutically or veterinarily acceptable carrier. Other active

materials may also be present, as may be considered appropriate or advisable for the disease or condition being treated or prevented.

5 The carrier, or, if more than one be present, each of the carriers, must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

10 The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an orally administered formulation. The formulations may conveniently be presented in unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

15 Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising 20 bringing a compound of general formulae (I) or (II) in conjunction or association with a pharmaceutically or veterinarianly acceptable carrier or vehicle.

25 Formulations for oral administration in the present invention may be presented as: discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion; or as a bolus etc.

30 For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example

corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate 5 stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more 10 accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be 15 formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose 20 and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

Parenteral formulations will generally be sterile.

According to a sixth aspect of the invention, there is provided a process for the 25 preparation of a pharmaceutical or veterinary composition as described above, the process comprising bringing the active compound(s) into association with the carrier, for example by admixture.

Preferred features for each aspect of the invention are as for each other aspect *mutatis* 30 *mutandis*.

The invention will now be illustrated with the following examples:

Solution Phase Chemistry – General Methods

All solvents were purchased from ROMIL Ltd (Waterbeach, Cambridge, UK) at SpS 5 or Hi-Dry grade unless otherwise stated. General peptide synthesis reagents were obtained from Chem-Impex Intl. Inc. (Wood Dale IL 60191. USA). Thin layer chromatography (TLC) was performed on pre-coated plates (Merck aluminium sheets silica 60 F254, part no. 5554). Visualisation of compounds was achieved under ultraviolet light (254nm) or by using an appropriate staining reagent. Flash 10 column purification was performed on silica gel 60 (Merck 9385). All analytical HPLC were obtained on Phenomenex Jupiter C₄, 5 μ , 300A, 250 x 4.6mm, using mixtures of solvent A = 0.1%aq trifluoroacetic acid (TFA) and solvent B = 90% acetonitrile / 10% solvent A on automated Agilent systems with 215 and / or 254nm UV detection. Unless otherwise stated a gradient of 10 – 90% B in A over 25 15 minutes at 1.5mL / min was performed for full analytical HPLC analysis. HPLC-MS analysis was performed on an Agilent 1100 series LC/MSD, using automated Agilent HPLC systems, with a gradient of 10 – 90% B in A over 10 minutes on Phenomenex Columbus C₈, 5 μ , 300A, 50 x 2.0mm at 0.4mL / min. Nuclear magnetic resonance (NMR) were obtained on a Bruker DPX400 (400MHz 1H frequency; QXI probe) in 20 the solvents and temperature indicated. Chemical shifts are expressed in parts per million (δ) and are referenced to residual signals of the solvent. Coupling constants (J) are expressed in Hz.

Solid Phase Chemistry – General Methods

25

Example inhibitors (1-156) were prepared through a combination of solution and solid phase Fmoc-based chemistries (see 'Solid Phase Peptide Synthesis', Atherton, E. and Sheppard, R. C., IRL Press Ltd, Oxford, UK, 1989, for a general description). An appropriately protected and functionalised building block was prepared in 30 solution (e.g. general compound (19), Scheme 1), then reversibly attached to the solid phase through an appropriate linker. Rounds of coupling / deprotection / chemical modification e.g. oxidation were then performed until the full length

desired molecule was complete (Scheme 2). Example inhibitors (1-156) were then released (cleaved) from the solid phase, analysed, purified and assayed for inhibition versus a range of proteases.

5 Generally, multipins (polyamide 1.2 → 10μmole loadings, see www.mimotopes.com) were used for the solid phase synthesis, although any suitable solid phase surface could be chosen. In general, the 1.2μmole gears were used to provide small scale crude examples for preliminary screening, whilst the 10μmole crowns were used for scale-up synthesis and purification of preferred examples.

10 Standard coupling and Fmoc deprotection methods were employed (see Grabowska, U. *et al*, *J. Comb. Chem.* 2(5), 475-490, 2000. for a thorough description of solid phase multipin methodologies).

Preparation of Initial Assembly

15 Building Block-linker constructs (e.g.(21), typically 100mg to 2g) were carboxyl activated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HBTU, 1 mole equivalent), 1-hydroxybenzotriazole.hydrate (HOBT, 1 mole equivalent) and N-methylmorpholine (NMM, 2 mole equivalents) in dimethylformamide (DMF, typically 1 to 10mL) for 5 minutes. Amino functionalised DA/MDA crowns or HEMA gears (10μmole per crown / 1.2μmole per gear, 0.33 mole equivalent of total surface amino functionalisation compared to activated construct) were added, followed by additional DMF to cover the solid phase surface. The loading reaction was left overnight. Following overnight loading, 20 crowns / gears were taken through standard cycles washing, Fmoc deprotection and loading quantification (see Grabowska, U. *et al*) to provide loaded Building Block-linker constructs (e.g.(22)). Analysis indicated virtually quantitative loading in all examples.

25

Coupling Cycles

The coupling of standard Fmoc-aminoacids (10 or 20 mole equivalent) were performed via carboxyl activated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HBTU, 10 or 20mole equivalent), 1-hydroxybenzotriazole.hydrate (HOBT, 10 or 20mole equivalent) and N-methylmorpholine (NMM, 20 or 40mole equivalents) in dimethylformamide, with pre-activation for 5 minutes. Activated species were dispensed to the appropriate wells of a polypropylene 96-well plate (Beckman, 1mL wells, 500 μ L solution per well for crowns or 250 μ L solution per well for gears) in a pattern required for synthesis. Loaded free amino Building Block-linker constructs (e.g.(22)) were added and the coupling reaction left overnight. Following overnight coupling, crowns / gears were taken through standard cycles washing and Fmoc deprotection (see Grabowska, U. *et al*). Identical activation and coupling conditions were used for the coupling of a range of carboxylic acids (R-COOH). Alternatively, chloroformates e.g. morpholine-4-carbonylchloride (10mole equivalent), were coupled in DMF with the addition of NMM (10mole equivalents).

Acidolytic Cleavage Cycle

A mixture of 95% TFA / 5% water was pre-dispensed into two polystyrene 96-well plates (Beckman, 1mL wells, 600 μ L solution per well for crowns or 300 μ L solution per well for gears) in a pattern corresponding to that of the synthesis. The completed multipin assembly was added to the first plate (mother plate), the block covered in tin foil and cleaved for 2 hours. The cleaved multipin assembly was then removed from the first plate and added to the second plate (washing plate) for 15 minutes. The spent multipin assembly was then discarded and the mother / washing plates evaporated on an HT-4 GeneVac plate evaporator.

Analysis and Purification of Cleaved Examples

(a) Ex 1.2 μ mole Gears. 100 μ L dimethylsulphoxide (DMSO) was added to each post cleaved and dried washing plate well, thoroughly mixed, transferred to the corresponding post cleaved and dried mother plate well and again thoroughly

mixed. 10 μ L of this DMSO solution was diluted to 100 μ L with a 90% acetonitrile / 10% 0.1%aq TFA mixture. 20 μ L aliquots were analysed by HPLC-MS and full analytical HPLC. In each case the crude example molecules gave the expected [M + H]⁺ ion and an HPLC peak at > 80% (by 215nm UV analysis).

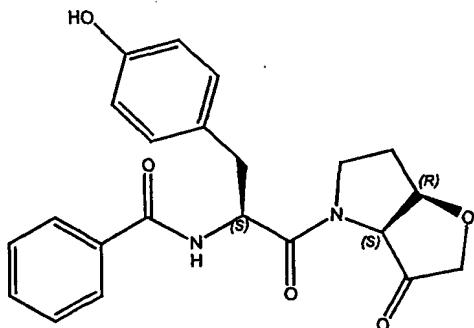
5 This provided an approximately 10mM DMSO stock solution of good quality crude examples for preliminary protease inhibitory screening.

(b) Ex 10 μ mole Crowns. 500 μ L of a 90% acetonitrile / 10% 0.1%aq TFA mixture was added to each washing plate well, thoroughly mixed, transferred to the corresponding mother plate well and again thoroughly mixed. 5 μ L of this 10 solution was diluted to 100 μ L with a 90% acetonitrile / 10% 0.1%aq TFA mixture. 20 μ L aliquots were analysed by HPLC-MS and full analytical HPLC. In each case the crude example molecules gave the expected [M + H]⁺ ion and an HPLC peak at > 80% (by 215nm UV analysis). The polystyrene blocks containing crude examples were then lyophilised.

15 (c) Individual examples (ex (b)) were re-dissolved in a 1 : 1 mixture of 0.1% aq TFA / acetonitrile (1mL) and purified by semi-preparative HPLC (Phenomenex Jupiter C₄, 5 μ , 300A, 250 x 10mm, a 25-90% B in A gradient over 25mins, 4.0mL/min, 215nm UV detection). Fractions were lyophilised into pre-tarred glass sample vials to provide purified examples (typically 2 to 4mg, 40 to 80% yield).

20 (d) Purified examples were dissolved in an appropriate volume of DMSO to provide a 10mM stock solution, for accurate protease inhibitory screening.

EXAMPLE 1. (An example of general formula (I)). (3aS, 6aR) N-[1S-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro [3,2-*b*]pyrrol-4-yl)ethyl]benzamide



Following the general details from Scheme 1, the required bicyclic building block (3a*S*,6a*R*) 3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid 9*H*-fluoren-9-yl methyl ester (**19**) was prepared in 8 steps as follows.

5

(1) Preparation of (2*S*,3*S*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester.

Trans-3-hydroxy-L-proline (10.0g, 76.3mmole) was added to a vigorously stirred, ice-cooled solution of sodium carbonate (16.90g, 160.2mmole) in water (100mL). 1,4-Dioxan (75mL) was added providing an opaque but mobile mixture. 9-Fluorenylmethyl chloroformate (20.31g, 80mmole) in 1,4-dioxan (75mL) was added over 1hr, then the ice-cooling removed and the mixture stirred at RT for an additional 2hr. Additional water (300mL) was added, the reaction mixture washed with chloroform (2 x 250mL) and the combined organic layers discarded. The aqueous phase was acidified with 1N HCl to ~ pH 2, providing a thick opaque mixture. The acidified aqueous mixture was extracted with chloroform (2 x 500mL) and the now clear aqueous phase discarded. The opaque combined chloroform layers were dried (Na₂SO₄), filtered and reduced in vacuo to provide batch 1 (5.70g). The residual precipitate (a mixture of product and drying agent) was triturated with hot methanol (2 x 250mL) and the combined methanol solutions reduced in vacuo to provide batch 2 (10.25g). Batch 1 and 2 were individually analysed by TLC (single UV spot, R_f = 0.15, 20% MeOH in CHCl₃), and HPLC-MS (single main UV peak with R_t = 7.069mins, 354.2 [M + H]⁺, 376.2 [M + Na]⁺) and found to be identical, giving a combined yield of 15.95g (45.2mmole, 59.2%). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

¹H (DMSO-d₆ at 298K); 1.80-2.02 (2H_{*y*}, m), 3.49-3.62 (2H_{*δ*}, m), 4.12-4.38 (H_{*α*}, H_{*β*}, Fmoc H-9 and CH₂, m), 5.55/5.62 (OH), 7.30-7.31 (2H aromatic, Fmoc H-2 and H-7), 7.35-7.37 (2H aromatic, Fmoc H-3 and H-6), 7.43-7.45 (2H aromatic, Fmoc H-1 and H-8), 7.63-7.65 (2H aromatic, Fmoc H-4 and H-5), 12.8-13.0 (COOH).

^1H NMR (CDCl_3 at 298K); 31.70/32.70 (d, C_γ), 44.68/45.32 (d, C_δ), 46.94/46.97 (u, Fmoc C-9), 67.04/67.33 (d, Fmoc CH_2), 68.24/68.51 (u, C_α), 73.12/74.23 (u, C_β), 120.49/120.52 (u, Fmoc C-4 and C-5), 125.49/125.58 (u, Fmoc C-1 and C-8), 127.50 (u, Fmoc C-2 and C-7), 128.04 (u, Fmoc C-3 and C-6), 140.99/141.09 (q, Fmoc C-4' and C-5'), 144.02/144.16 (q, Fmoc C-1' and C-8'), 154.33/154.54 (q, OCON), 172.10/172.39 (COOH).
5

(2) Preparation of (2S,3S) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

10 (2S,3S) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester (10.9g, 30.8mmole) was dissolved in toluene (75mL) in a Dean-Stark apparatus. Allyl alcohol (20mL) was added followed by *p*-toluenesulphonic acid hydrate (6.05g, 31.4mmole). The mixture was refluxed for 1hr, cooled and CHCl_3 (300mL) added. The organic layer was washed with NaHCO_3 (300mL), 0.1N HCl (300mL) and brine (300mL), then dried (Na₂SO₄). Filtration and reduction in vacuo gave a pale yellow foam (13.5g).
15 The crude foam was purified over silica gel (150g) eluting with a gradient of heptane : ethyl acetate 3:1 → 1:1. Desired fractions were combined and reduced in vacuo to a colourless gum yield 10.34g (26.3mmole, 85.4%). TLC (single UV spot, R_f = 0.30, heptane : ethyl acetate 1:1), analytical HPLC R_t = 18.849mins, HPLC-MS (single main UV peak with R_t = 8.354mins, 394.2 [M + H]⁺, 416.2 [M + Na]⁺). Analysis by ^1H and ^{13}C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.
20

25 ^1H NMR (CDCl_3 at 298K); 2.00-2.21 (2H $_\gamma$, m), 2.70/2.85 (OH , b), 3.72-3.81 (2H $_\delta$, m), 4.12-4.67 (H $_\alpha$, H $_\beta$, Fmoc H-9 and CH_2 , 2 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, m), 5.20-5.40 (2 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, m), 5.82-5.99 (1 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, m), 7.28-7.33 (2H aromatic, Fmoc H-2 and H-7), 7.34-7.41 (2H aromatic, Fmoc H-3 and H-6), 7.53-7.66 (2H aromatic, Fmoc H-1 and H-8), 7.77-7.81 (2H aromatic, Fmoc H-4 and H-5).

30 ^{13}C NMR (CDCl_3 at 298K); 32.28/33.04 (d, C_γ), 44.98/45.32 (d, C_δ), 47.56/47.63 (u, Fmoc C-9), 66.44 (d, $\text{COOCH}_2\text{CH}=\text{CH}_2$), 68.01/68.11 (d, Fmoc CH_2), 68.32/68.72 (u, C_α), 74.49/75.67 (u, C_β), 119.20/119.48 (d,

COOCH₂CH=CH₂), 120.34/120.37 (u, Fmoc C-4 and C-5), 125.36/125.60 (u, Fmoc C-1 and C-8), 127.47 (u, Fmoc C-2 and C-7), 128.06/128.12 (u, Fmoc C-3 and C-6), 131.79/131.94 (u, COOCH₂CH=CH₂), 141.65/141.71 (q, Fmoc C-4' and C-5'), 144.12/144.34 (q, Fmoc C-1' and C-8'), 155.13/155.59 (q, OCON), 170.53/170.55 (COOCH₂CH=CH₂).

5 (3) Preparation of (2*S*,3*R*) (3-formyloxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

10 Triphenylphosphine (2.76g, 10.5mmole, TPP) was dissolved in dry tetrahydrofuran (75mL), under a nitrogen blanket with stirring and ice-cooled. Diisopropylazodicarboxylate (2.12g, 2.07mL, 10.5mmole, DIAD) was added dropwise over 15mins to give a precipitous white mixture. (2*S*,3*S*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (4.15g, 10.5mmole) and formic acid (0.97g, 0.79mL, 15 21.0mmole) were mixed in dry tetrahydrofuran (30mL) and added over 15mins to the TPP/DIAD mixture. The reaction was stirred for a further 1hr at 0°C, then overnight at RT. The solvents were removed in vacuo to give a viscous pale yellow oil (11.1g). The crude oil was purified over silica gel (250g) eluting with a gradient of heptane : ethyl acetate 4:1 → 1:1. Product 20 fractions were identified and reduced in vacuo to give (2*S*,3*R*) (3-formyloxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester / Bis-hydrazide of DIAD, a white solid, yield 4.0g. TLC (single UV spot, R_f = 0.50, heptane : ethyl acetate 1:1), analytical HPLC R_t = 19.064mins, HPLC-MS (single main UV peak with R_t = 9.721mins, 422.2 25 [M + H]⁺, 444.1 [M + Na]⁺ and a non-UV peak with R_t = 5.057mins, 205.1 [M + H]⁺, 431.2 [2M + Na]⁺).

30 (4) Preparation of (2*S*,3*R*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

(2*S*,3*R*) (3-formyloxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester / Bis-hydrazide of DIAD mixture (4.0g) was dissolved in allyl alcohol (18mL), cH₂SO₄ (75μL) added and heated to reflux

for 90mins. The mixture was cooled, EtOAc (200mL) added and washed with NaHCO₃ (200mL), brine (200mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a viscous tan oil (4.2g). The crude oil was purified over silica gel (150g) eluting with a gradient of heptane : ethyl acetate 2:1 → 1:1. Desired fractions were combined and reduced in vacuo to a colourless gum yield 1.75g (4.44mmole, 42.4%). TLC (single UV spot, R_f = 0.25, heptane : ethyl acetate 1:1), analytical HPLC R_t = 17.795mins, HPLC-MS (single main UV peak with R_t = 8.574mins, 394.2 [M + H]⁺, 416.2 [M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans 5 geometrical isomers around the 3° amide bond.

10 ¹H (CDCl₃ at 298K); 2.09-2.19 (2H_γ, m), 2.52 (OH, dd, J 1.0, 6.0), 3.54-3.65/3.70-3.82 (2H_δ, m), 4.14-4.20/4.22-4.30 (Fmoc H-9, dm), 4.30-4.39 (1 x Fmoc CH₂, m), 4.43-4.58 (H_α + 1 x Fmoc CH₂, m), 4.60-4.65 (H_β, m) 4.65-4.76 (2 x COOCH₂CH=CH₂, m), 5.23-5.36 (2 x COOCH₂CH=CH₂, m), 5.81-6.00 (1 x COOCH₂CH=CH₂, m), 7.28-7.38 (2H aromatic, Fmoc H-2 and H-7), 7.39-7.46 (2H aromatic, Fmoc H-3 and H-6), 7.53-7.69 (2H aromatic, Fmoc H-1 and H-8), 7.73-7.81 (2H aromatic, Fmoc H-4 and H-5).

15 ¹³C (CDCl₃ at 298K); 32.34/33.22 (d, C_γ), 44.65/44.90 (d, C_δ), 47.57/47.63 (u, Fmoc C-9), 63.89/64.22 (u, C_α), 66.38/66.41 (d, COOCH₂CH=CH₂), 68.02 (d, Fmoc CH₂), 71.84/72.80 (u, C_β), 119.08/119.31 (d, COOCH₂CH=CH₂), 120.39 (u, Fmoc C-4 and C-5), 125.32/125.46/125.56 (u, Fmoc C-1 and C-8), 127.46 (u, Fmoc C-2 and C-7), 128.12 (u, Fmoc C-3 and C-6), 132.03/132.14 (u, COOCH₂CH=CH₂), 141.65/141.69 (q, Fmoc C-4' and C-5'), 144.00/144.16/144.43/144.48 (q, Fmoc C-1' and C-8'), 154.88/155.25 (q, OCON), 169.94/169.99 (COOCH₂CH=CH₂).

20 (5) Preparation of (2*S*,3*R*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.
(2*S*,3*R*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (1.75g, 4.45mmole) was dissolved in dry dichloromethane (20mL) in a 50mL glass pressure tube and cooled to -78°C. Isobutylene gas (~10mL) was condensed into the solution and cH₂SO₄

(100 μ L) added. A stirrer bar was added, the tube was sealed, the cooling removed and stirred at RT for 72hr. The sealed tube was cooled to -78°C, N-methylmorpholine (200 μ L, 1eq w.r.t. cH₂SO₄) and allowed to warm to RT, unsealed, with stirring over 2hr. Dichloromethane (75mL) was added and the 5 organics washed with NaHCO₃ (75mL), then brine (75mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a mobile pale tan oil (2.41g). The crude oil was purified over silica gel (150g) eluting with a gradient of heptane : ethyl acetate 4:1 \rightarrow 3:1. Desired fractions were combined and reduced in vacuo to a thick clear oil yield 1.66g (3.69mmole, 10 83.0%). TLC (single UV spot, R_f = 0.45, heptane : ethyl acetate 2:1), analytical HPLC Rt = 22.811mins, HPLC-MS (single main UV peak with Rt = 11.193mins, 450.2 [M + H]⁺, 472.2 [M + Na]⁺, 921.4 [2M + Na]⁺).

15 (6) Preparation of (2*S*,3*R*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester.
20 (2*S*,3*R*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (1.60g, 3.56mmole) was dissolved in dry dichloromethane (20mL) with stirring. Tetrakis(triphenylphosphine) palladium (0) (83mg, 0.071mmole, 0.02eq) was added, followed by phenyltrihydrosilane (0.77g, 0.674mL, 7.12mmole, 2eq). After 2hr, dichloromethane (150mL) was added and the organics washed with 0.01N HCl (150mL), brine (150mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a dark grey solid (2.14g). The crude solid was purified over silica gel (75g) eluting with a gradient of heptane : ethyl acetate 2:1 \rightarrow 1:6. Desired fractions were combined and reduced in vacuo to a white 25 crystalline yield 0.89g (2.17mmole, 61.1%). TLC (single UV spot, R_f = 0.30, heptane : ethyl acetate 1:2), analytical HPLC Rt = 19.135mins, HPLC-MS (single main UV peak with Rt = 9.386mins, 354.1 [M + H-Bu¹]⁺, 410.2 [M + H]⁺, 432.1 [M + Na]⁺, 841.1 [2M + Na]⁺). Analysis by ¹H and ¹³C NMR 30 showed the presence of cis and trans geometrical isomers around the 3° amide bond.

⁵ δ H (CDCl₃ at 298K); 1.23 (9H, s), 1.98-2.28 (2H_y, m), 3.40-3.50 (1H₆, m), 3.68-3.81 (1H₆, m), 4.10-4.50 (H_a + H_b + Fmoc H-9 + 2 x Fmoc CH₂, m), 7.29-7.40 (2H aromatic, Fmoc H-2 and H-7), 7.42-7.47 (2H aromatic, Fmoc H-3 and H-6), 7.55-7.70 (2H aromatic, Fmoc H-1 and H-8), 7.73-7.85 (2H aromatic, Fmoc H-4 and H-5), 6.30-8.30 (COOH, b).

¹H NMR (δ , CDCl₃ at 298K); 28.285 (u, (CH₃)C), 31.47/32.29 (d, C_γ), 44.13/44.38 (d, C_δ), 47.51/47.60 (u, Fmoc C-9), 62.73/62.95 (u, C_α), 67.96/68.13 (d, Fmoc CH₂), 71.77/72.67 (u, C_β), 120.33 (u, Fmoc C-4 and C-5), 125.39 /125.50/125.55/125.61 (u, Fmoc C-1 and C-8), 127.46 (u, Fmoc C-2 and C-7), 128.01/128.07 (u, Fmoc C-3 and C-6), 141.58/141.66 (q, Fmoc C-4' and C-5'), 144.04/144.23/144.46 (q, Fmoc C-1' and C-8'), 154.95/155.32 (q, OCON), 175.19/175.65 (COOH).

(7) Preparation of (2*S*,3*R*)-*(3-tert-butoxy)-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid 9*H*-fluoren-9-ylmethyl ester.*

(2S,3R) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester (615mg, 1.5mmole) was dissolved with stirring in dry dichloromethane (15mL). The reaction was flushed with nitrogen and cooled to -15°C. Isobutylchloroformate (225mg, 1.6mmole in dry dichloromethane (2.5mL) and N-methylmorpholine (303mg, 3.0mmole in dry dichloromethane (2.5mL) were added simultaneously in 0.5mL aliquots over 15mins. Ethereal diazomethane (generated from diazald (4.7g, ~15mmole in diethyl ether (75mL)) onto sodium hydroxide (5.25g) in water (7.5mL) / ethanol (15mL) at 60°C). was added to the activated aminoacid solution and stirred at RT for 24hr. Acetic acid (~2mL) was added to quench the reaction, then *tert*-butylmethylether (150mL) was added, the organics washed with water (3 x 200mL), then dried (Na₂SO₄). The solvents were removed in vacuo to give a thick yellow oil (890g). The crude oil was purified over silica gel (75g) eluting with a gradient of heptane : ethyl acetate 3:1 → 2:1. Desired fractions were combined and reduced in vacuo to give (2S,3R) (3-*tert*-butoxy)-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester, a pale yellow solid, yield 270mg (0.624mmole, 41.6%). TLC (single UV spot, R_f =

0.55, heptane : ethyl acetate 1:1), analytical HPLC Rt = 20.085mins, HPLC-MS (2 main UV peaks with Rt = 7.48mins, 350.1 [M + H]⁺, 372.1 [M + Na]⁺, 721.0 [2M + Na]⁺ and Rt = 9.949mins, 406.2 [M + H-N₂]⁺, 456.2 [M + Na]⁺, 889.3 [2M + Na]⁺).

5 Note that upon HPLC-MS analysis, m/z 350.1 corresponds to the desired bicycle product (3aS, 6aR) 3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (19).

10 (8) Cyclisation to (3aS, 6aR) 3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (19).

15 A solution of lithium chloride (205mg, 4.8mmole) in water (1.25mL) and acetic acid (5.0mL) was added to (2S,3R) (3-*tert*-butoxy)-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (209mg, 0.483mmole). Gas was evolved and the yellow oily solid dissolved over 1hr to give a virtually colourless solution. After 90mins, chloroform (150mL) was added and the organics washed with NaHCO₃ (2 x 150mL), brine (150mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a thick yellow gum (200mg). The crude gum was purified over silica gel (40g) eluting with a gradient of heptane : ethyl acetate 3:2 → 1:1. Desired fractions were combined and reduced in vacuo to a white crystalline solid, yield 133mg (0.38mmole, 18.6% from starting acid). TLC (single UV spot, R_f = 0.25, heptane : ethyl acetate 1:1), analytical HPLC broad peak Rt = 15.2-17.6mins, HPLC-MS (single broad UV peak with Rt = 7.45-8.56mins, 350.1 [M + H]⁺, 372.1 [M + Na]⁺, 721.2 [2M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

30 ¹H (CDCl₃ at 298K); 1.61-1.97 (2H_γ, m), 3.32-3.45 (1H_δ, m), 3.66-3.75/3.85-3.95 (1/2H_δ + 1/2H_δ, dm), 3.95/4.10 (1 x COCH_{2α} + 1 x COCH_{2β}, dm), 4.15-4.30 (Fmoc H-9 + 2 x Fmoc CH₂, m), 4.40-4.60 / 4.80-4.92 (H_α + H_β, complex), 7.20-7.30 (2H aromatic, Fmoc H-2 and H-7), 7.31-7.42 (2H aromatic, Fmoc H-3 and H-6), 7.50-7.57/7.60-7.66 (2H aromatic, Fmoc H-1 and H-8), 7.68-7.76 (2H aromatic, Fmoc H-4 and H-5).

5 ^1C (CDCl₃ at 298K); 31.76/32.28 (d, C_γ), 45.59/45.95 (d, C_δ), 47.64 (u, Fmoc C-9), 62.26/62.77 (u, C_α), 68.03/68.65 (d, Fmoc CH₂), 71.28 (d, COCH₂), 82.17/83.11 (u, C_β), 120.38 (u, Fmoc C-4 and C-5), 125.41 /125.59 /125.88 (u, Fmoc C-1 and C-8), 127.45/127.49 (u, Fmoc C-2 and C-7), 128.13 (u, Fmoc C-3 and C-6), 141.73 (q, Fmoc C-4' and C-5'), 144.16/144/37/144.88 (q, Fmoc C-1' and C-8'), 155.33 (q, OCON), 209.32 (COCH₂).

10 Following the general details from Scheme 2, the required bicyclic building block (3aS, 6aR) 3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (19) was converted to building block-linker construct (21) as follows:

15 (3aS, 6aR) 3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (19) (100mg, 0.286mmole) was dissolved in a mixture of ethanol (5.0mL) and water (0.75mL) containing sodium acetate trihydrate (59mg, 0.428mmole, 1.5eq). 4-[[(hydrazinocarbonyl)amino] methyl]cyclohexanecarboxylic acid trifluoroacetate (95mg, 0.286mmole, 1.0eq, Murphy, A. M. *et al*, *J. Am. Chem. Soc.*, 114, 3156-3157, 1992) was added and the mixture refluxed for 90mins. Chloroform (50mL) was added and the organics washed with HCl (50mL, ~ pH3), dried (Na₂SO₄) and reduced in vacuo to provide crude building block-linker 20 construct (21) as a colourless gum. Yield 172mg, analytical HPLC 2 peaks Rt = 16.477 and 18.512mins (cis / trans geometrical isomers), HPLC-MS (2 x UV peak with Rt = 7.75 and 8.82mins, 547.3 [M + H]⁺, 569.3 [M + Na]⁺). Crude (21) was used directly for construct loading.

25 Following the general details from Scheme 2, the required building block-linker construct (21) was attached to the solid phase providing loaded building block-linker construct (22) as follows:

30 Building block-linker construct (21) (0.26mmoles), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate (HBTU, 98.6mg, 0.26mmole), 1-hydroxybenzotriazole hydrate and (HOBT, 39.8mg, 0.26mmole) were dissolved in dimethylformamide (3mL) and N-methylmorpholine (NMM, 58μL, 0.52mmole)

added. After pre-activation for 5 minutes, free amine gears (72 x 1.2 μ mole) were added, followed by dimethylformamide (5.5mL) and left overnight. The spent coupling solution was then added to free amine crowns (10 x 10 μ mole) and left overnight. Standard washing and analyses indicated quantitative loading.

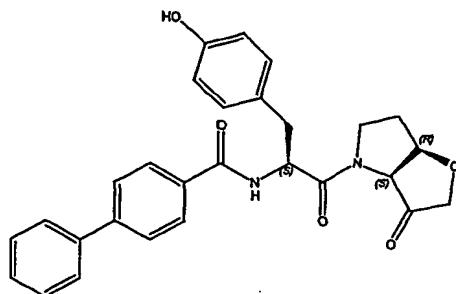
5

Following the general details from Scheme 2, the required loaded building block-linker construct (22) was elaborated on the solid phase as follows:

10 Loaded construct (22) was elaborated to EXAMPLE 1 (3aS, 6aR) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide by standard Fmoc deprotection and sequential coupling with Fmoc-Tyr(OBut)-OH then benzoic acid. The crude example was cleaved and analysed (see general techniques). HPLC Rt = 10.15mins (>95%), HPLC-MS 395.1 [M + H]⁺.

15 The following examples (2 – 82) were prepared as detailed for EXAMPLE 1, coupling with the required reagents to provide the full length molecule.

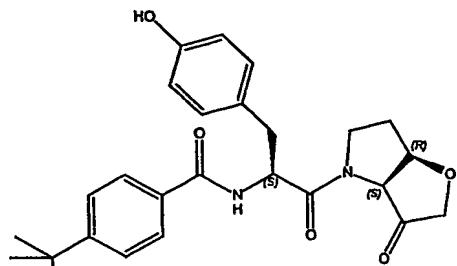
EXAMPLE 2. (3aS, 6aR) Biphenyl-4-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



20

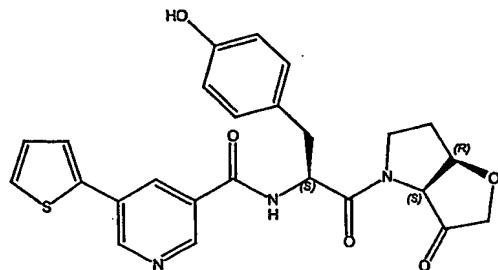
HPLC Rt = 14.94-15.46mins (> 90%), HPLC-MS 471.2 [M + H]⁺.

EXAMPLE 3. (3aS, 6aR) 4-*tert*-Butyl-*N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 15.29-15.89mins (> 90%), HPLC-MS 451.3 [M + H]⁺

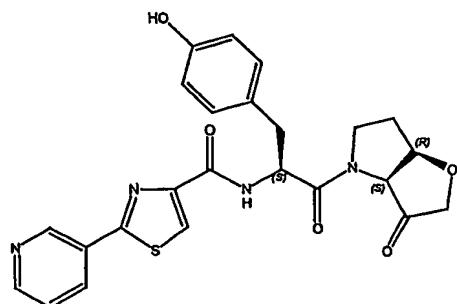
EXAMPLE 4. (3aS, 6aR) N-[1S-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)ethyl]-5-thiophen-2-ylnicotinamide



HPLC Rt = 11.12 mins (> 90%), HPLC-MS 478.2 [M + H]⁺

10

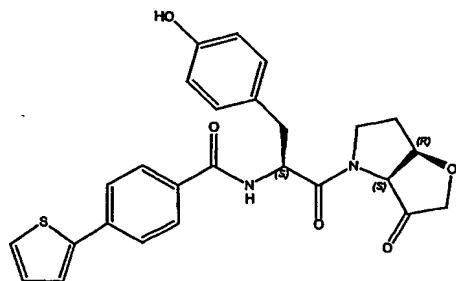
EXAMPLE 5. (3aS, 6aR) 2-Pyridin-3-ylthiazole-4-carboxylic acid [1S-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyrrol-4-yl)ethyl]amide



HPLC Rt = 8.58mins (> 90%), HPLC-MS 479.2[M + H]⁺

EXAMPLE 6. (3a*S*, 6a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

5

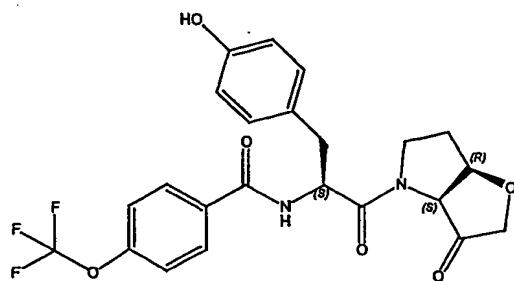


HPLC Rt = 14.77-15.31mins (> 90%), HPLC-MS 477.2 [M + H]⁺

EXAMPLE 7. (3a*S*, 6a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-trifluoromethoxybenzamide

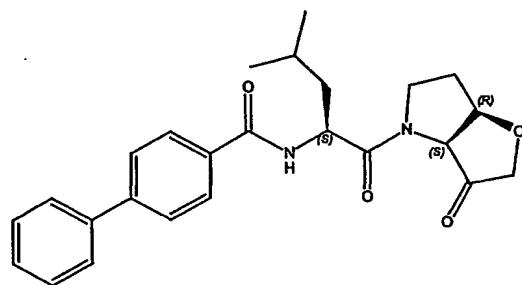
10

15



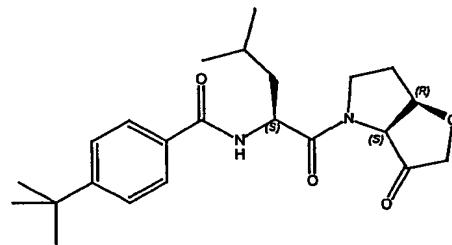
HPLC Rt = 14.68mins (> 90%), HPLC-MS 479.2 [M + H]⁺

EXAMPLE 8. (3a*S*, 6a*R*) Biphenyl-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



5 HPLC Rt = 16.90-18.04mins (> 90%), HPLC-MS 421.3 [M + H]⁺

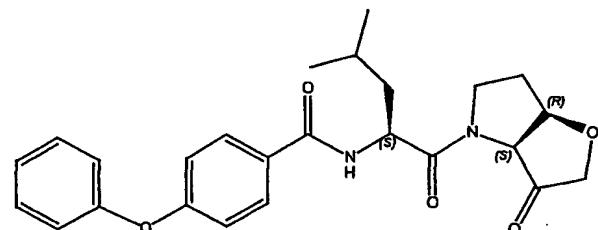
EXAMPLE 9. (3a*S*, 6a*R*) 4-*tert*-Butyl-N-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide



10

HPLC Rt = 17.45-18.62mins (> 90%), HPLC-MS 401.2 [M + H]⁺

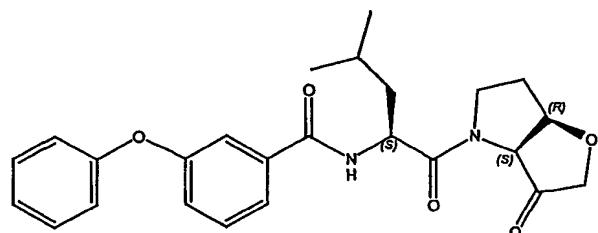
EXAMPLE 10. (3a*S*, 6a*R*) N-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-phenoxybenzamide



15

HPLC Rt = 17.26-18.38mins (> 90%), HPLC-MS 437.2 [M + H]⁺

EXAMPLE 11. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-3-phenoxybenzamide

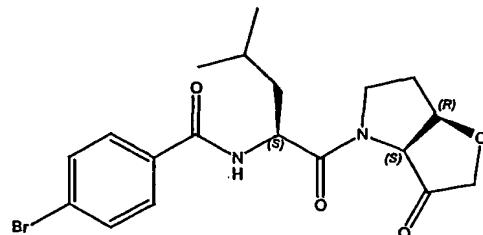


5

HPLC Rt = 17.34-18.52mins (> 90%), HPLC-MS 437.2 [M + H]⁺

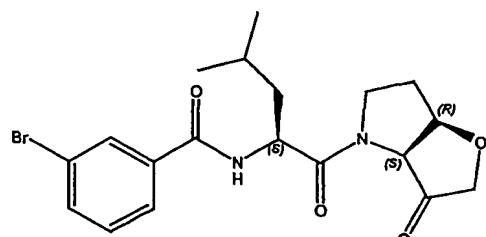
EXAMPLE 12. (3a*S*, 6a*R*) 4-Bromo-*N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

10



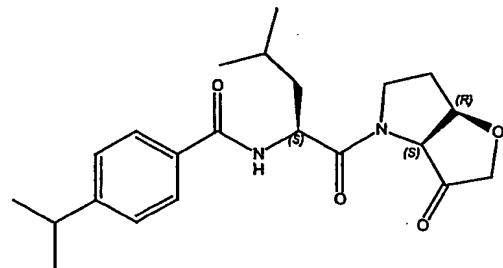
HPLC Rt = 14.81mins (> 90%), HPLC-MS 423.2 / 425.2 [M + H]⁺

15 EXAMPLE 13. (3a*S*, 6a*R*) 3-Bromo-*N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide



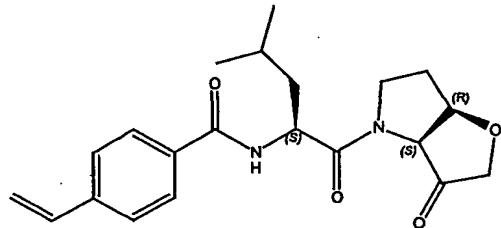
HPLC Rt = 14.85-16.20mins (> 90%), HPLC-MS 423.2 / 425.2 [M + H]⁺

EXAMPLE 14. (3a*S*, 6a*R*) 4-Isopropyl-*N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide



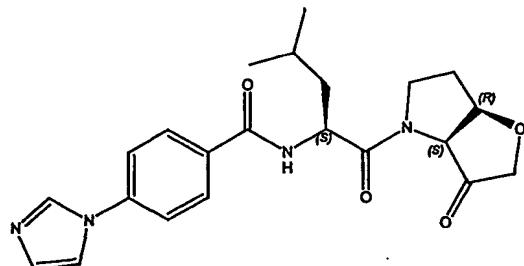
HPLC Rt = 16.41-17.65mins (> 90%), HPLC-MS 387.2 [M + H]⁺

EXAMPLE 15. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-vinylbenzamide



HPLC Rt = 14.63mins (> 90%), HPLC-MS 371.1 [M + H]⁺

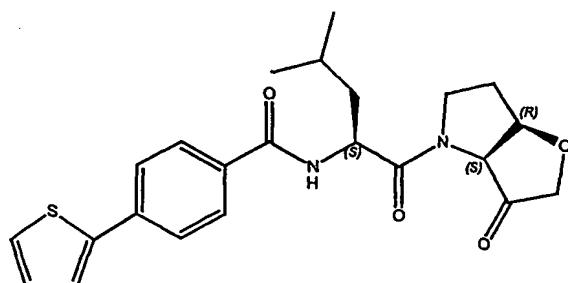
EXAMPLE 16. (3a*S*, 6a*R*) 4-Imidazol-1-yl-*N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide



HPLC Rt = 9.20mins (> 90%), HPLC-MS 411.2 [M + H]⁺

EXAMPLE 17. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-

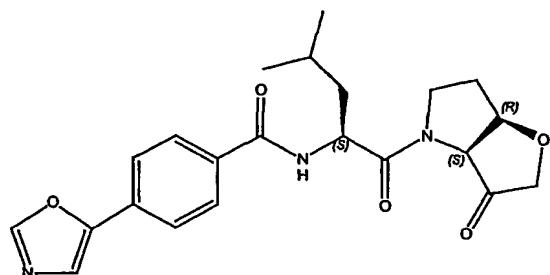
5 carbonyl) butyl]-4-thiophen-2-ylbenzamide



HPLC Rt = 16.49-18.34mins (> 90%), HPLC-MS 427.2 [M + H]⁺

EXAMPLE 18. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-

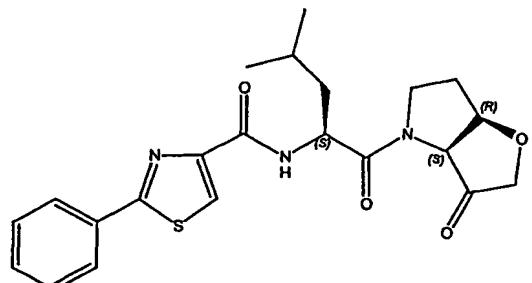
10 carbonyl) butyl]-4-oxazol-5-ylbenzamide



HPLC Rt = 12.79mins (> 90%), HPLC-MS 412.2 [M + H]⁺

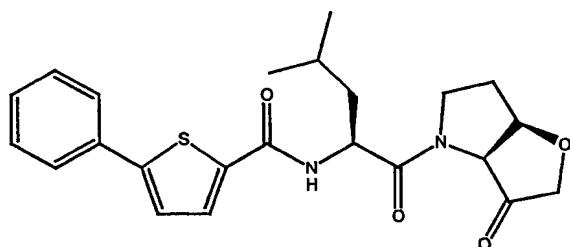
EXAMPLE 19. (3a*S*, 6a*R*) 2-Phenylthiazole-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide

15



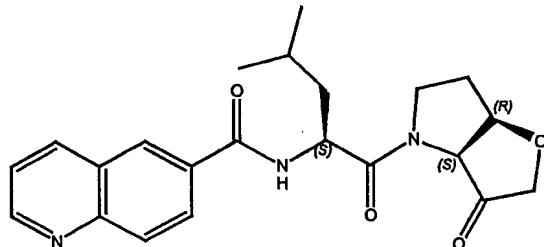
HPLC Rt = 16.41-17.80mins (> 90%), HPLC-MS 428.2 [M + H]⁺

EXAMPLE 20. (3a*S*, 6a*R*) 5-Phenylthiophene-2-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



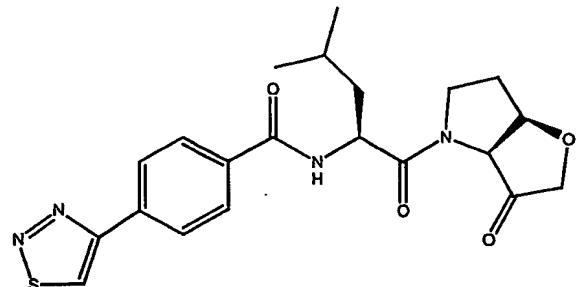
HPLC Rt = 16.89mins (> 90%), HPLC-MS 427.2 [M + H]⁺

EXAMPLE 21. (3a*S*, 6a*R*) Quinoline-6-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



HPLC Rt = 9.08mins (> 90%), HPLC-MS 396.2 [M + H]⁺

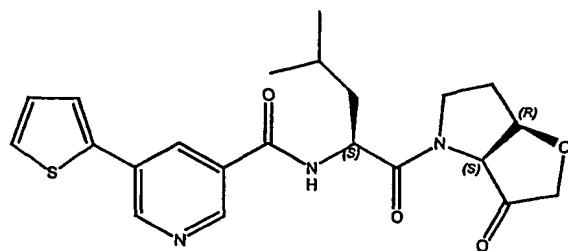
EXAMPLE 22. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-4-[1,2,3]thiadiazol-4-ylbenzamide



HPLC Rt = 13.41mins (> 90%), HPLC-MS 429.2 [M + H]⁺

EXAMPLE 23. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-5-thiophen-2-ylnicotinamide

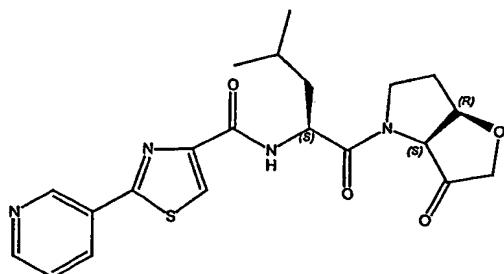
5



HPLC Rt = 13.24mins (> 90%), HPLC-MS 428.2 [M + H]⁺

EXAMPLE 24. (3a*S*, 6a*R*) 2-Pyridin-3-ylthiazole-4-carboxylic acid [3-methyl-1*S*-(3-

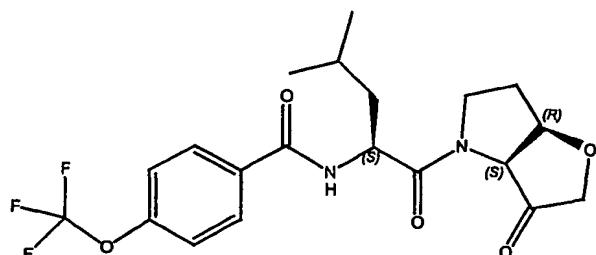
10 oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



HPLC Rt = 10.22mins (> 90%), HPLC-MS 429.2 [M + H]⁺

EXAMPLE 25. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-

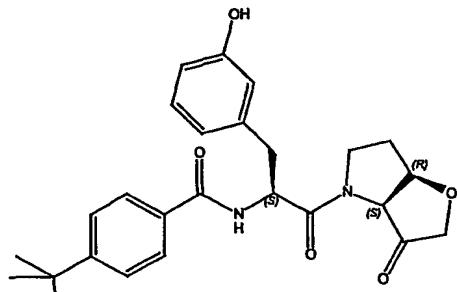
15 carbonyl) butyl]-4-trifluoromethoxybenzamide



-145-

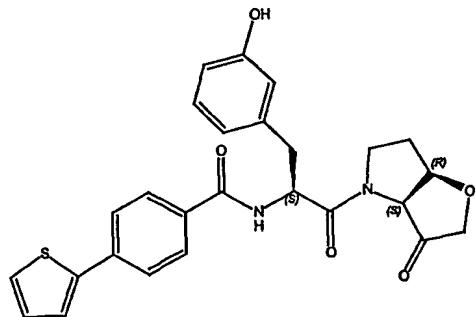
HPLC Rt = 16.90-18.34mins (> 90%), HPLC-MS 429.2 [M + H]⁺

EXAMPLE 26. (3a*S*, 6a*R*) 4-*tert*-Butyl-N-[1*S*-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



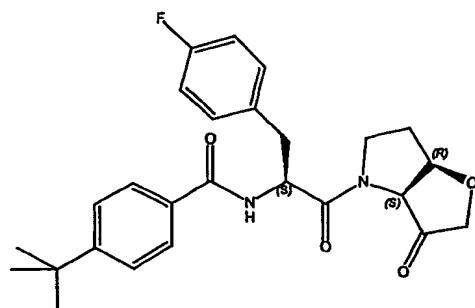
5 HPLC Rt = 16.14-17.02mins (> 90%), HPLC-MS 451.2 [M + H]⁺

EXAMPLE 27. (3a*S*, 6a*R*) N-[1*S*-(3-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide



10 HPLC Rt = 15.31-16.07mins (> 90%), HPLC-MS 477.2 [M + H]⁺

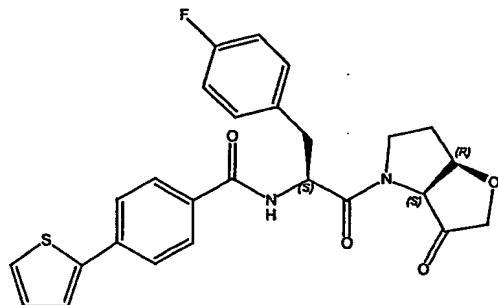
EXAMPLE 28. (3a*S*, 6a*R*) 4-*tert*-Butyl-N-[1*S*-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 18.37-19.63mins (> 90%), HPLC-MS 453.1 [M + H]⁺

EXAMPLE 29. (3a*S*, 6a*R*) *N*-[1*S*-(4-fluorobenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-4-thiophen-2-ylbenzamide

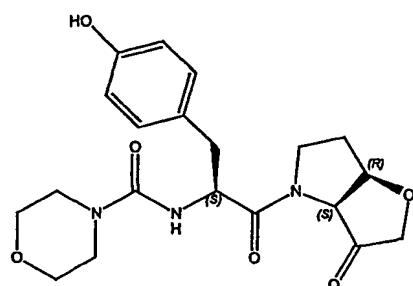
5



HPLC Rt = 17.45-18.59mins (> 90%), HPLC-MS 479.2 [M + H]⁺

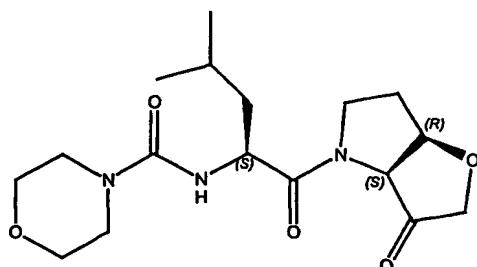
EXAMPLE 30. (3a*S*, 6a*R*) Morpholine-4-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

10



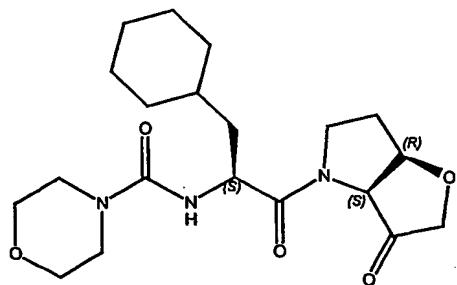
HPLC Rt = 7.38mins (>95%), HPLC-MS 404.2 [M + H]⁺.

15 EXAMPLE 31. (3a*S*, 6a*R*) Morpholine-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



HPLC-MS 354.2 [M + H]⁺.

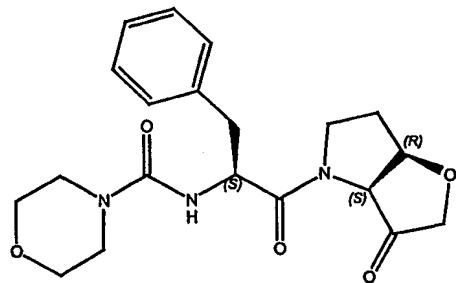
EXAMPLE 32. (3a*S*, 6a*R*) Morpholine-4-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



5

HPLC-MS 394.2 [M + H]⁺.

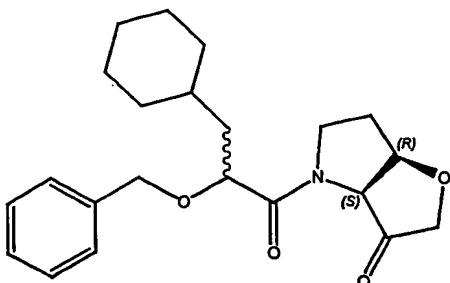
EXAMPLE 33. (3a*S*, 6a*R*) Morpholine-4-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-oxo- hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



10

HPLC Rt = 10.07mins (>95%), HPLC-MS 388.1 [M + H]⁺.

EXAMPLE 34. (2*RS*, 3a*S*, 6a*R*) 4-(2-Benzylxyloxy-3-[cyclohexyl]propionoyl)tetra 15 hydrofuro[3,2-*b*]pyrrol-3-one.



HPLC Rt = 17.5-19.7mins (>90%), HPLC-MS 372.4 [M + H]⁺, 390.3 [M + H + 18]⁺.

(a) Preparation of 3-Cyclohexyl-2S-hydroxypropionic acid (Compound (25) Scheme 4)

5

A solution of sodium nitrite (12.1g, 175mmol) in water (40ml) was added dropwise to a stirred suspension of (S)- α -aminocyclohexanepropionic acid hydrate (5g, 26.5mmol) in 0.5M sulphuric acid (120ml, 60mmol) at 0°C over 1.5hours. The mixture was allowed to warm to ambient temperature over 20hours. The product was extracted into diethyl ether (2 x 25ml) then the ethereal layers were washed with saturated aqueous sodium chloride solution (2 x 25ml), dried (Na₂SO₄) and the solvents removed *in vacuo*. The residue (5.3g) was recrystallized from diethyl ether (10ml) and heptane (25ml) to give 3-cyclohexyl-2S-hydroxypropionic acid as a white solid, yield 2.4 g, (53%).

10

15 δ_H (400MHz, CDCl₃ at 298K), 0.89-1.35 (5H, m) and 1.51-1.86 (7H, m) (OCHCH₂ and cyclohexyl), 4.32 (1H, OCHCH₂, m)

(b) Preparation of 2RS-Benzylxy-3-cyclohexylpropionic acid (Compound (26)

20 Scheme 4)

Sodium hydride (265mg of 60% dispersion in oil, 6.6mmol) was added in two portions to a stirred mixture of 3-cyclohexyl-2S-hydroxypropionic acid (0.52g, 3.0mmol), dimethylformamide (5ml) and dichloromethane (5ml) at 0°C over 25 5minutes. The mixture was stirred at 0°C for 5minutes then at ambient temperature for 45minutes. Benzyl bromide (0.45ml, 3.8mmol) was added then the mixture stirred for 1 hour before adding dimethylformamide (5ml). After stirring for 4 hours potassium iodide (50mg, 0.3mmol) was added. The mixture was stirred for 20hours then heated at 55°C for 1hour then allowed to cool to ambient temperature and 30 poured into water (15ml). A saturated aqueous sodium chloride solution (5ml) was added then the mixture was extracted with dichloromethane (5ml then 10ml) that was discarded. The aqueous layer was acidified using 1M hydrochloric acid (10 ml) then

extracted with dichloromethane (2 x 10ml). The dichloromethane layer was dried (MgSO₄) and the solvent removed *in vacuo*. The residue (0.55g) was dissolved in dimethylformamide (8ml) then cooled to 0°C before adding sodium hydride (190mg of 60% dispersion in oil, 4.75mmol). The mixture was stirred for 30 minutes then 5 polymer bound isocyanate (380mg, 2mmolNg⁻¹) added. The mixture was stirred for 2 hours at ambient temperature then poured into water (15ml). 1M Hydrochloric acid (10ml) was added then the product was extracted into dichloromethane (2 x 10ml), dried (Na₂SO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography over silica gel eluting with a gradient of methanol : dichloromethane 10 0:1 → 1:20. Appropriate fractions were combined and the solvents removed *in vacuo* to give 2*RS*-benzyloxy-3-cyclohexylpropionic acid as a colourless oil, yield 41mg (5.2%).

HPLC-MS (single main UV peak with Rt = 9.47mins, 261.2 [M - H]⁻, 285.2[M + Na]⁺, 547.3[2M + Na]⁺).

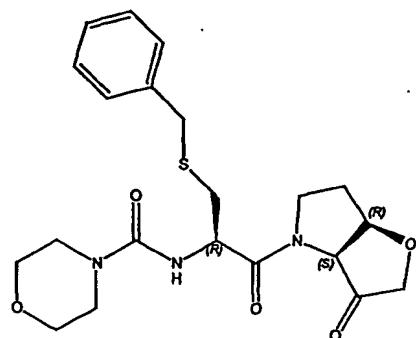
15

δ_{H} (400MHz, CDCl₃ at 298K), 0.72-1.03 (2H, cyclohexane, m), 1.08-1.38 (3H, cyclohexane, m), 1.45-1.93 (6H + 2H β , cyclohexane, m), 3.93-4.18 (1H α , OCH₂CO), 4.35-4.53 (1H, CH₂O, d, *J* = 11.52 Hz), 4.68-4.88 (1H, CH₂O, d, *J* = 11.54 Hz), 7.20-7.47 (5H, ArH, m), 9.36 (1H, OH, brs).

20

Compound (26) was coupled under standard conditions to loaded building block-linker construct (22), then cleaved to provide EXAMPLE 34.

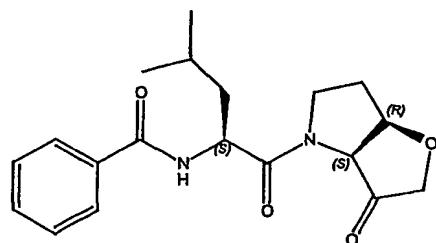
EXAMPLE 35. (3a*S*, 6a*R*) Morpholine-4-carboxylic acid [1*R*-benzylsulfanyl methyl-25 2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



HPLC Rt = 12.15mins (>95%), HPLC-MS 434.1 [M + H]⁺.

EXAMPLE 36. (3aS, 6aR) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-

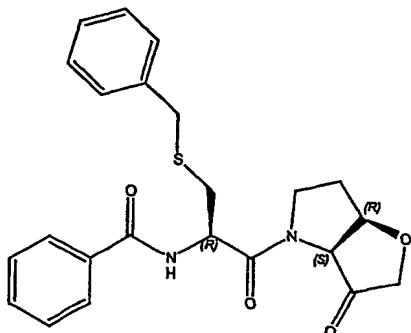
5 carbonyl) butyl]benzamide



HPLC Rt = 12.43mins (>95%), HPLC-MS 345.2 [M + H]⁺.

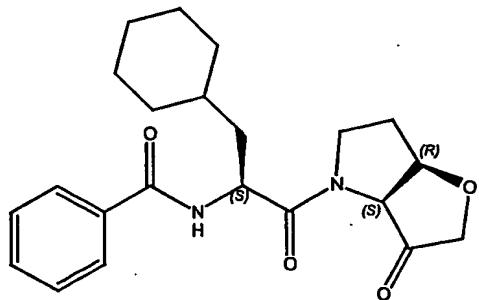
EXAMPLE 37. (3aS, 6aR) *N*-[1*R*-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydro

10 furo[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 15.09mins (>95%), HPLC-MS 425.1 [M + H]⁺.

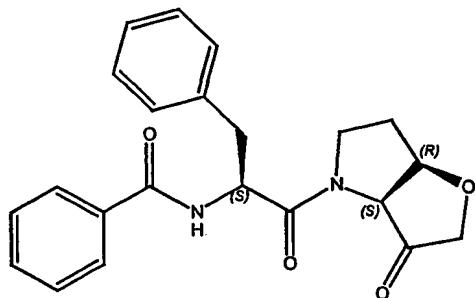
EXAMPLE 38. (3a*S*, 6a*R*) *N*-[1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 15.63mins (>90%), HPLC-MS 385.3 [M + H]⁺, 791.3 [2M + Na]⁺.

5

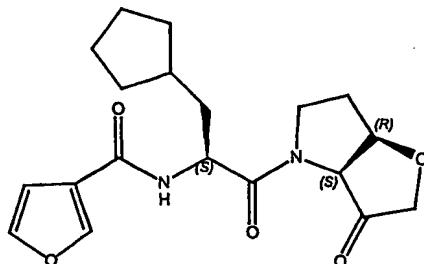
EXAMPLE 39. (3a*S*, 6a*R*) *N*-[1*S*-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 12.85mins (>90%), HPLC-MS 379.1 [M + H]⁺.

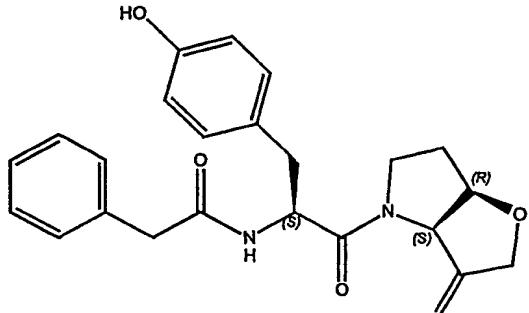
10

EXAMPLE 40. (3a*S*, 6a*R*) Furan-3-carboxylic acid [1*S*-cyclopentylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



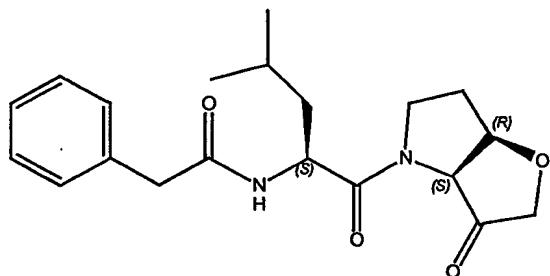
HPLC Rt = 13.23mins (>95%), HPLC-MS 361.2 [M + H]⁺.

EXAMPLE 41. (3a*S*, 6a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenylacetamide



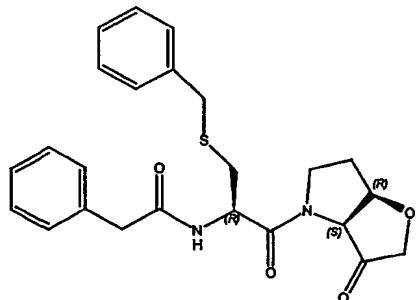
5 HPLC Rt = 10.71mins (>95%), HPLC-MS 409.1 [M + H]⁺.

EXAMPLE 42. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-2-phenylacetamide



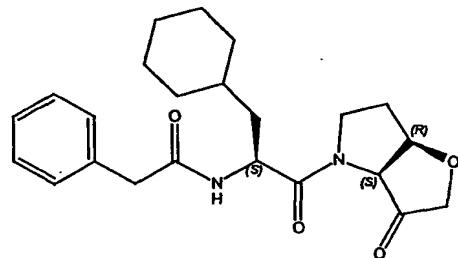
10 HPLC Rt = 13.00mins (>95%), HPLC-MS 359.2 [M + H]⁺.

EXAMPLE 43. (3a*S*, 6a*R*) *N*-[1*R*-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-2-phenylacetamide



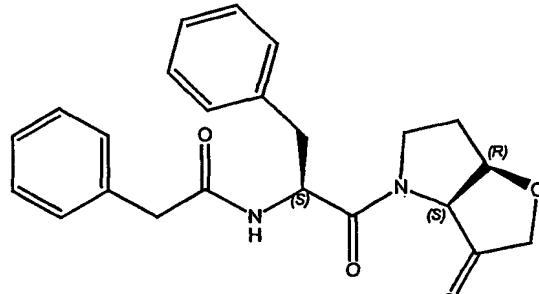
HPLC Rt = 15.53mins (>90%), HPLC-MS 439.1 [M + H]⁺.

EXAMPLE 44. (3a*S*, 6a*R*) *N*-[1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-
5 *b*]pyrrol-4-yl)ethyl]-2-phenylacetamide



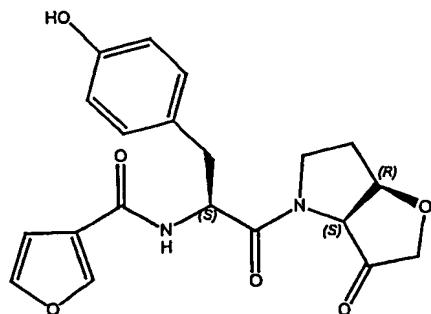
HPLC Rt = 18.5mins (>90%), HPLC-MS 399.2 [M + H]⁺.

EXAMPLE 45. (3a*S*, 6a*R*) *N*-[1*S*-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-
10 *b*]pyrrol-4-yl)ethyl]-2-phenylacetamide



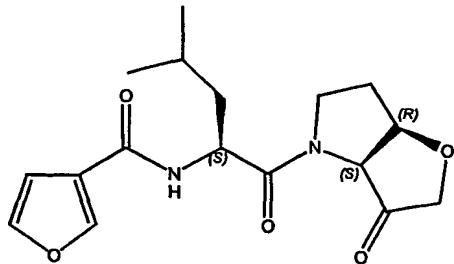
HPLC Rt = 13.2mins (>90%), HPLC-MS 393.2 [M + H]⁺.

EXAMPLE 46. (3a*S*, 6a*R*) Furan-3-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



HPLC Rt = 8.65mins (>95%), HPLC-MS 385.2 [M + H]⁺.

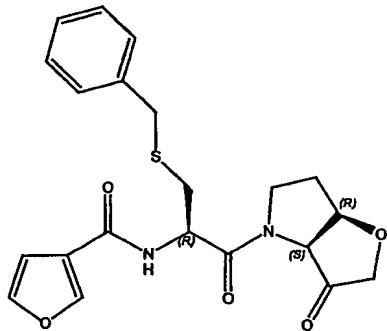
EXAMPLE 47. (3a*S*, 6a*R*) Furan-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



5

HPLC Rt = 10.95mins (>90%), HPLC-MS 335.1 [M + H]⁺, 357.1 [M + Na]⁺.

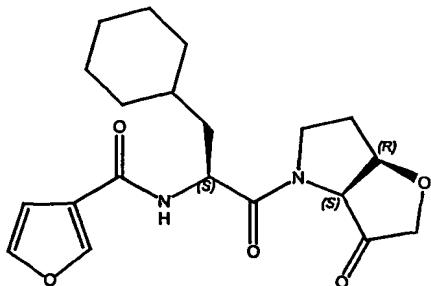
EXAMPLE 48. (3a*S*, 6a*R*) Furan-3-carboxylic acid [1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



10

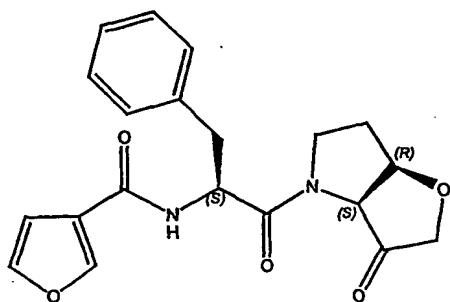
HPLC Rt = 13.68mins (>90%), HPLC-MS 415.1 [M + H]⁺.

EXAMPLE 49. (3a*S*, 6a*R*) Furan-3-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



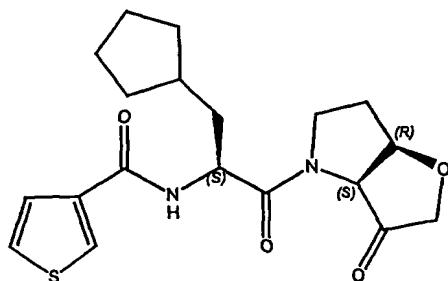
HPLC Rt = 14.39mins (>90%), HPLC-MS 375.2 [M + H]⁺, 771.3 [2M + Na]⁺.

EXAMPLE 50. (3a*S*, 6a*R*) Furan-3-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-oxo-hexa
5 hydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



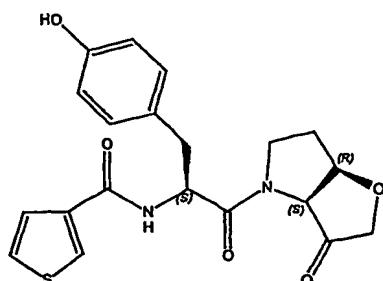
HPLC Rt = 11.51mins (>90%), HPLC-MS 369.1 [M + H]⁺.

EXAMPLE 51. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [1*S*-cyclopentylmethyl-2-
10 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



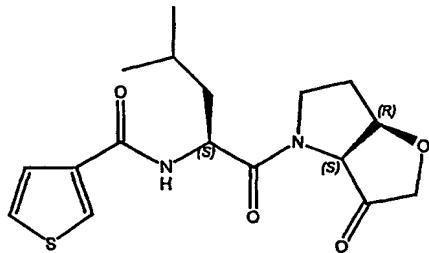
HPLC Rt = 14.07mins (>95%), HPLC-MS 377.3 [M + H]⁺.

EXAMPLE 52. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-
15 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



HPLC Rt = 11.75mins (>95%), HPLC-MS 401.3 [M + H]⁺.

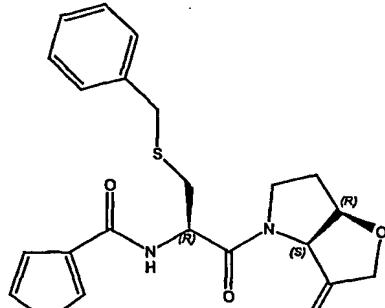
EXAMPLE 53. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexa hydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



5

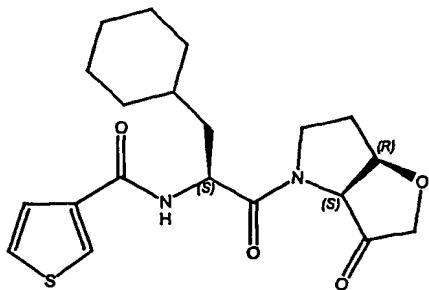
HPLC Rt = 14.01mins (>90%), HPLC-MS 351.1 [M + H]⁺, 373.1 [M + Na]⁺.

EXAMPLE 54. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [1*R*-benzylsulfanylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



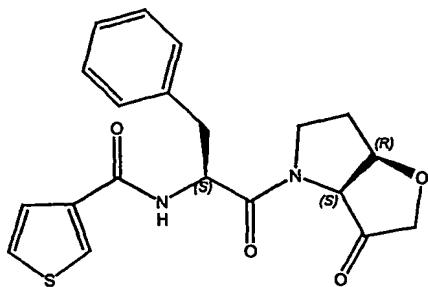
10 HPLC Rt = 14.51mins (>95%), HPLC-MS 431.1 [M + H]⁺.

EXAMPLE 55. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



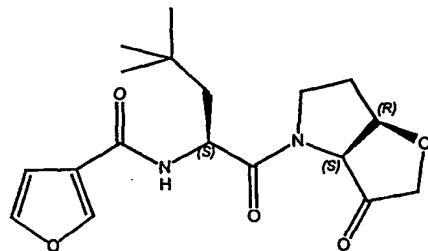
HPLC Rt = 15.11mins (>90%), HPLC-MS 391.1 [M + H]⁺, 803.3 [2M + Na]⁺.

EXAMPLE 56. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-oxo-5-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



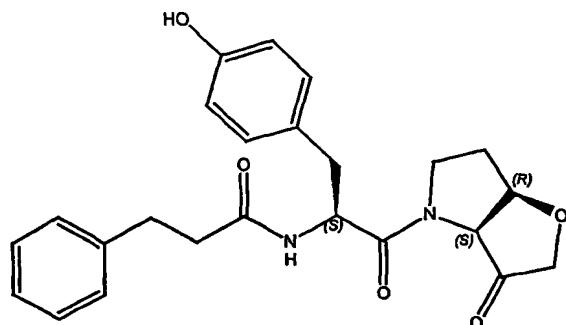
HPLC Rt = 12.27mins (>95%), HPLC-MS 385.1[M + H]⁺, 407.1 [M + Na]⁺, 791.2 [2M + Na]⁺.

EXAMPLE 57. (3a*S*, 6a*R*) Furan-3-carboxylic acid [3,3-dimethyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



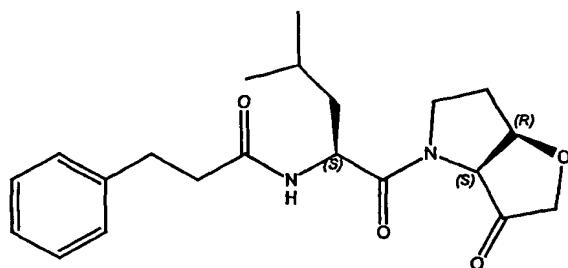
HPLC Rt = 12.50mins (>95%), HPLC-MS 349.2 [M + H]⁺.

EXAMPLE 58. (3a*S*, 6a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide



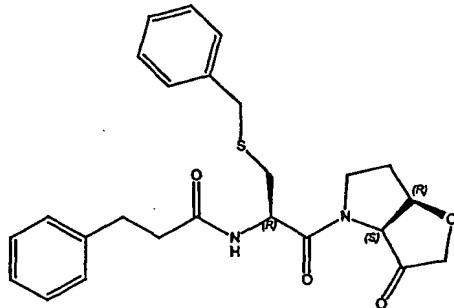
HPLC Rt = 11.72mins (>90%), HPLC-MS 423.2 [M + H]⁺.

EXAMPLE 59. (3a*S*, 6a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]-3-phenylpropionamide



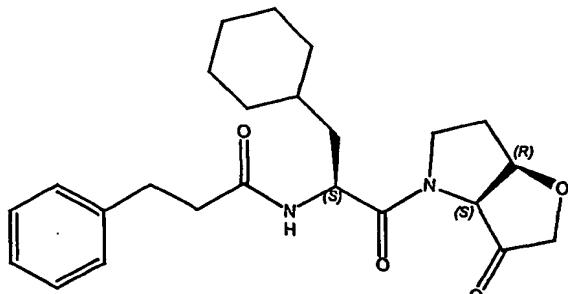
HPLC Rt = 13.46mins (>90%), HPLC-MS 373.1 [M + H]⁺, 767.3 [2M + Na]⁺.

EXAMPLE 60. (3a*S*, 6a*R*) *N*-[1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide



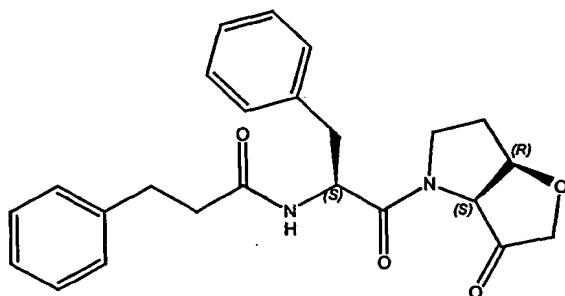
HPLC Rt = 16.22mins (>90%), HPLC-MS 453.2 [M + H]⁺, 475.0 [M + Na]⁺.

EXAMPLE 61. (3a*S*, 6a*R*) *N*-[1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide



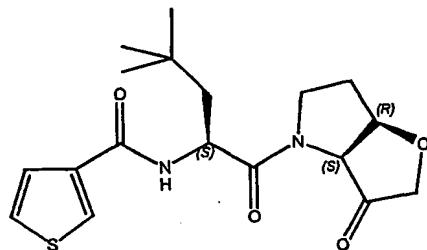
HPLC-MS 413.2 [M + H]⁺.

EXAMPLE 62. (3a*S*, 6a*R*) *N*-[1*S*-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-
5 *b*]pyrrol-4-yl)ethyl]-3-phenylpropionamide



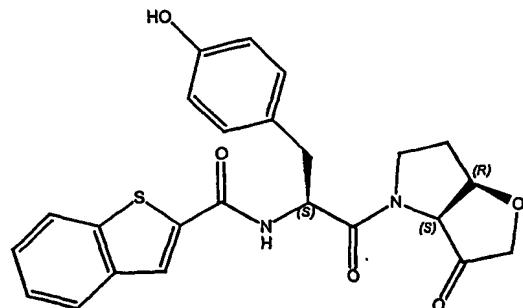
HPLC Rt = 16.68mins (>90%), HPLC-MS 407.2 [M + H]⁺, 835.2 [2M + Na]⁺.

EXAMPLE 63. (3a*S*, 6a*R*) Thiophene-3-carboxylic acid [3,3-dimethyl-1*S*-(3-oxo-
10 hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



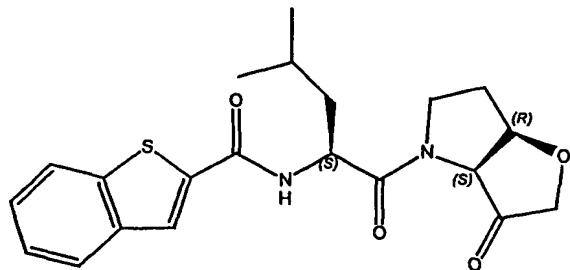
HPLC Rt = 13.24mins (>95%), HPLC-MS 365.2 [M + H]⁺.

EXAMPLE 64. (3a*S*, 6a*R*) Benzo[*b*]thiophene-2-carboxylic acid [1*S*-(4-hydroxy-
15 benzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



HPLC Rt = 13.10mins (>85%), HPLC-MS 451.1 $[M + H]^+$, 923.2 $[2M + Na]^+$.

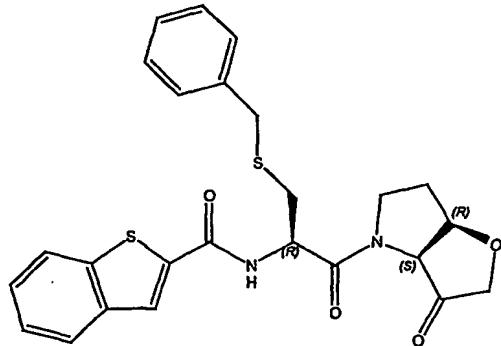
EXAMPLE 65. (3a*S*, 6a*R*) Benzo[*b*]thiophene-2-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



5

HPLC Rt = 15.62mins (>90%), HPLC-MS 401.1 $[M + H]^+$, 823.2 $[2M + Na]^+$.

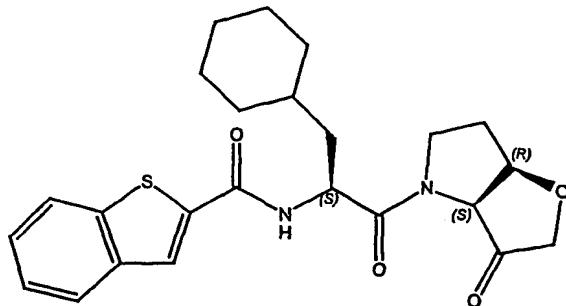
EXAMPLE 66. (3a*S*, 6a*R*) Benzo[*b*]thiophene-2-carboxylic acid [1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



10

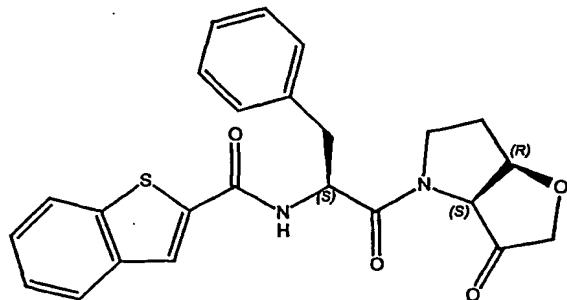
HPLC Rt = 17.47mins (>90%), HPLC-MS 481.1 $[M + H]^+$, 983.2 $[2M + Na]^+$.

EXAMPLE 67. (3a*S*, 6a*R*) Benzo[*b*]thiophene-2-carboxylic acid [1*S*-cyclohexyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



HPLC Rt = 18.15mins (>90%), HPLC-MS 441.2 [M + H]⁺, 903.2 [2M + Na]⁺.

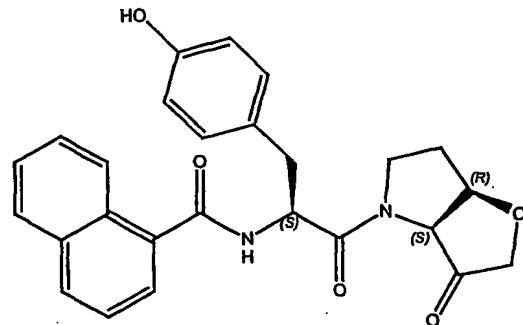
EXAMPLE 68. (3a*S*, 6a*R*) Benzo[*b*]thiophene-2-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



5

HPLC Rt = 15.58mins (>85%), HPLC-MS 435.1 [M + H]⁺, 891.2 [2M + Na]⁺.

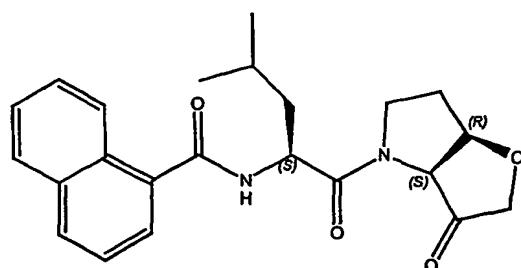
EXAMPLE 69. (3a*S*, 6a*R*) Naphthalene-1-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide



10

HPLC Rt = 12.42mins (>85%), HPLC-MS 445.1 [M + H]⁺, 911.3 [2M + Na]⁺.

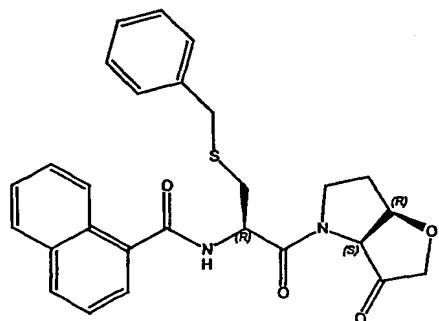
EXAMPLE 70. (3a*S*, 6a*R*) Naphthalene-1-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]amide



HPLC Rt = 14.81mins (>85%), HPLC-MS 395.2 [M + H]⁺, 811.3 [2M + Na]⁺.

EXAMPLE 71. (3a*S*, 6a*R*) Naphthalene-1-carboxylic acid [1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

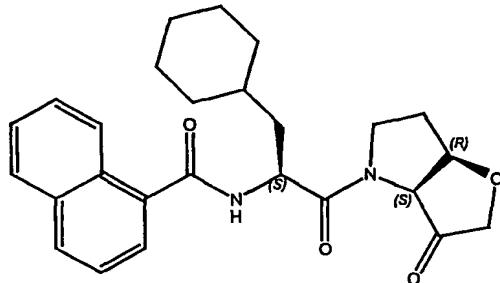
5



HPLC Rt = 17.10mins (>90%), HPLC-MS 475.2 [M + H]⁺.

EXAMPLE 72. (3a*S*, 6a*R*) Naphthalene-1-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

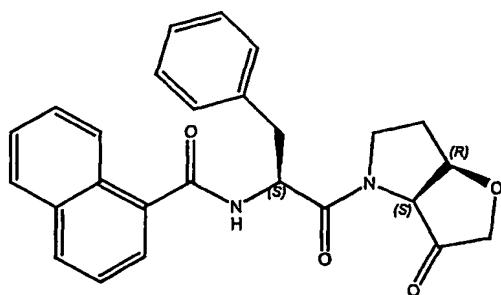
10



HPLC Rt = 17.45mins (>90%), HPLC-MS 435.2 [M + H]⁺, 891.4 [2M + Na]⁺.

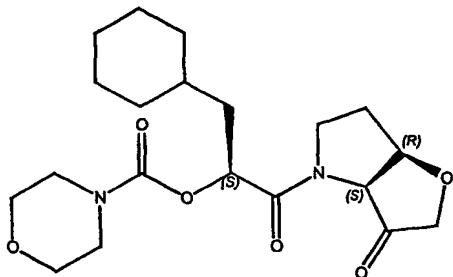
EXAMPLE 73. (3a*S*, 6a*R*) Naphthalene-1-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]amide

15



HPLC Rt = 15.17mins (>90%), HPLC-MS 429.1 [M + H]⁺, 879.3 [2M + Na]⁺.

EXAMPLE 74. (1*S*, 3*aS*, 6*aR*) Morpholine-4-carboxylic acid 1-cyclohexylmethyl-2-
5 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl ester



HPLC-MS 395.2 [M + H]⁺, 811.4 [2M + Na]⁺.

10 (a) Preparation of 3-cyclohexyl-2*S*-hydroxypropionic acid methyl ester. (Compound
(32), Scheme 6)

15 Trimethylsilyl chloride (1.78ml, 14.0mmol) was added dropwise to a stirred solution of 3-cyclohexyl-2*S*-hydroxypropionic acid (compound (25) 1.31g, 7.6mmol) in methanol (35ml). The mixture was stirred at room temperature for 20hours then the solvents were removed *in vacuo* to leave a pale yellow oil (1.38g). The crude oil was purified by chromatography over silica gel eluting with a gradient of n-heptane : ethyl acetate (4:1) Appropriate fractions were combined and the solvents removed *in vacuo* to give 3-cyclohexyl-2*S*-hydroxypropionic acid methyl ester as a colourless oil, yield 1.26 g, (89%). HPLC-MS (single main peak with Rt = 7.43mins, 187.14 [M + H]⁺, 395.2 [2M + Na]⁺).

20 δ_H (400MHz, CDCl₃ at 298K), 0.84-1.04 (2H, CH₂(cyclohexane), m), 1.09-1.36 (3H, CH₂(cyclohexane), CH (cyclohexane), m), 1.45-1.77 (7H, CH₂(cyclohexane),
25 CH(cyclohexane), m), 1.80-1.90 (1H β , m), 2.72 (1H, OH, d, *J* = 5.99 Hz), 3.80 (3H, CH₃O, s), 4.20-4.31 (1H α , m).

(b) Preparation of morpholine-4-carboxylic acid 1-carboxy-2-cyclohexylethyl ester (Compound (33), Scheme 6)

5 A solution of phosgene (33.6ml, 20% in toluene) was added to 3-cyclohexyl-2S-hydroxypropionic acid methyl ester (compound (32), 0.7 g, 4.03mmol) followed by 6 drops of dimethylformamide. The mixture was stirred at ambient temperature for 16hours then the solvents removed *in vacuo*. The residue was azeotroped with toluene (3 x 20ml), and dissolved in anhydrous dichloromethane (11ml). The 10 solution was cooled to 0°C then morpholine (0.86g, 9.85mmol) added. The mixture was stirred for 2 hours then partitioned between dichloromethane (30ml) and 0.5M hydrochloric acid (30ml). The dichloromethane layer was washed with saturated aqueous sodium hydrogen carbonate solution (30ml), saturated aqueous sodium chloride solution (30ml), dried (Na_2SO_4) and the solvent removed *in vacuo*. The 15 residue was purified by chromatography over silica gel eluting with ethyl acetate : heptane 1:1. Appropriate fractions were combined and the solvents removed *in vacuo* to leave morpholine-4-carboxylic acid 2-cyclohexyl-1-methoxycarbonylethyl ester (0.13g, 10%) as an oil. A solution of lithium hydroxide monohydrate (17.5mg, 0.418mmol) in water (0.76ml) was added to an iced-water chilled solution of 20 morpholine-4-carboxylic acid 2-cyclohexyl-1-methoxycarbonylethyl ester (110mg, 0.367mmol) in dioxane (1.5ml). The mixture was stirred at ambient temperature for 1hour then diluted with water (10ml). The aqueous layer was extracted with diethyl ether (2 x 10ml) which was discarded, then acidified to pH = 2 with 6M hydrochloric acid. The product was extracted into diethyl ether (2 x 10ml), then the combined 25 ethereal layers washed with saturated aqueous sodium chloride (10ml), dried (MgSO_4) and the solvent removed *in vacuo* to give morpholine-4-carboxylic acid 1-carboxy-2S-cyclohexylethyl ester as a white solid, yield 0.11g, (100% from ester). TLC (single spot, R_f = 0.20, methanol : dichloromethane 1:9), HPLC-MS (single main peak with R_t = 7.614mins, 286.2 $[\text{M} + \text{H}]^+$, 287.2 $[\text{M} + 2\text{H}]^+$, 593.3 $[\text{2M} + \text{Na}]^+$).

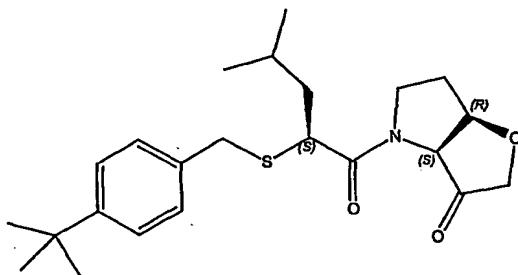
δ_H (400MHz, $CDCl_3$ at 298K), 0.75-1.00 (2H, CH_2 (cyclohexane), m), 1.02-1.28 (4H, CH_2 (cyclohexane), m), 1.33-1.46 (1H, CH (cyclohexane), m), 1.50-1.79 (6H, CH_2 (cyclohexane), m), 3.28-3.73 (8H, CH_2OCH_2 and CH_2NCH_2 , m), 4.92-5.02 (1H α , m), 5.99 (1H, OH, brs).

5

Compound (33) was coupled under standard conditions to loaded building block-linker construct (22), then cleaved to provide EXAMPLE 74.

EXAMPLE 75. ($3aS, 6aR$) 4-[2-(4-*tert*-butylbenzylsulfanyl)-4-methylpentanoyl]

10 tetrahydrofuro[3,2-*b*]pyrrol-3-one



HPLC Rt = 21.3-23.4mins (>80%), HPLC-MS 404.4 $[M + H]^+$.

(a) Preparation of 2*R*-Bromo-4-methylpentanoic acid (Compound (28), Scheme 5)

15

A solution of sodium nitrite (5.1g, 73mmol) in water (15ml) was added drop-wise at 0°C over 5 hours to a stirred mixture of D-leucine (8.75g, 67mmol), potassium bromide (29.75g, 0.25mol) and concentrated sulphuric acid (8.6ml) in water (100ml). The mixture was stirred for 30 minutes at 0°C then at ambient temperature for 20 hours. The product was extracted into diethyl ether (2 x 150ml) then the combined ethereal layers were washed with saturated aqueous sodium chloride solution (2 x 100ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography over silica gel eluting with a gradient of methanol : dichloromethane 1:50 → 1:20. Appropriate fractions were combined and the solvents removed *in vacuo* to leave 2*R*-bromo-4-methylpentanoic acid (28) as a colourless oil,

25

yield 1.60 g, (12.3%). TLC (single spot, R_f = 0.2, methanol : dichloromethane 1:20). Additionally, a second crop (5.2g, 40%) of slightly impure product was obtained

5 δ_H (400MHz, $CDCl_3$ at 298K), 0.95 and 0.99 (both 3H, CH_3CH , d, J = 6.55Hz), 1.77-1.89 (1H, CH_3CH , m), 1.93 (2H β , m), 4.31 (1H α , t, J = 7.7Hz), 9.3 (1H, CO_2H , brs).

(b) Preparation of 2*S*-(4-*tert*-butylbenzylsulfanyl)-4-methylpentanoic acid (Compound (30), Scheme 5)

10

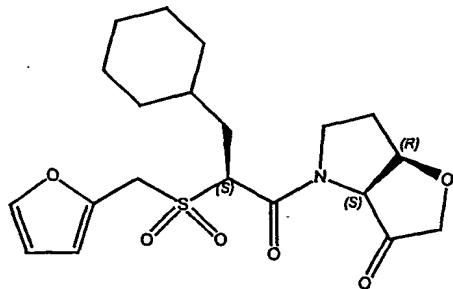
A solution of 2*R*-bromo-4-methylpentanoic acid (compound (28), 1.1g, 5.6mmol) and (4-(*tert*-butyl)phenyl)methanethiol (1.0g, 5.6mmol) in dimethylformamide (15ml) was purged with nitrogen for 5 minutes then cooled to 0°C. Triethylamine (0.79ml, 5.7mmol) was added drop-wise over 1 minute then the mixture was stirred 15 for two days at ambient temperature. The solvents were removed *in vacuo* and residue purified by flash chromatography over silica gel eluting with a gradient of methanol : dichloromethane 0:1 → 1:20. Appropriate fractions were combined and the solvents removed *in vacuo* to leave a residue which was purified by flash chromatography over silica gel eluting with ethyl acetate : heptane 2:5. Appropriate 20 fractions were combined and the solvents removed *in vacuo* to give 2*S*-(4-*tert*-butylbenzylsulfanyl)-4-methylpentanoic acid (30) as a colourless oil, yield 150 mg, (9%). TLC (single spot, R_f = 0.2, heptane : ethyl acetate 5:2), analytical HPLC with main peak R_t = 22.117mins, HPLC-MS (main UV peak with R_t = 11.072mins, 317.2 [M + Na]⁺).

25

δ_H (400MHz, $CDCl_3$ at 298K), 0.70 and 0.85 (both 3H, CH_3CH , d, J = 6.3), 1.29 (9H, $(CH_3)_3C$, s), 1.44-1.51 (1H, CH_3CH , m), 1.62-1.75 (2H β , m), 3.15-3.20 (1H α , m), 3.81 and 3.88 (both 1H, SCH_2 , d, J = 13.2Hz), 7.25-7.35 (4H, aromatic).

30 Compound (30) was coupled under standard conditions to loaded building block-linker construct (22), then cleaved to provide EXAMPLE 75.

EXAMPLE 76. (3a*S*, 6a*R*) 4-[3-Cyclohexyl-2*S*-(furan-2-ylmethanesulphonyl) propionyl]tetrahydrofuro[3,2-*b*]pyrrol-3-one



5 HPLC Rt = 12.8 – 15.1mins (>90%), HPLC-MS 410.1 [M + H]⁺, 841.2 [2M + Na]⁺.

(a) Preparation of (*R*)- α -bromocyclohexanepropionic acid

A solution of sodium nitrite (0.45g, 6.5mmol) in water (1.2ml) was added dropwise 10 at 0°C over 4 hours to a stirred mixture of (*R*)- α -aminocyclohexanepropionic acid (1g, 5.8mmol), potassium bromide (2.3g, 19.2mmol) and concentrated sulphuric acid (0.66ml) in water (7ml). The mixture was stirred for 5hours at 0°C then at ambient temperature for 16hours. The product was extracted into diethyl ether (4 x 20ml) then the combined ethereal layers were washed with saturated aqueous sodium 15 chloride solution (2 x 50ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by chromatography over silica gel eluting with a gradient of methanol : dichloromethane 1:50 → 1:20. Appropriate fractions were combined and the solvents removed *in vacuo* to give (*R*)- α -bromocyclohexanepropionic acid as a pale yellow oil 0.374 g, (27%). TLC (single spot, R_f = 0.45, 10% methanol in 20 dichloromethane), HPLC-MS (single main peak with Rt = 8.88mins, 234.1 / 236.1 [M + H]⁺, 257.2 / 259.2 [M + Na]⁺).

δ_H (400MHz, $CDCl_3$ at 298K), 0.83-1.88 (11H, CH (cyclohexane), CH_2 (cyclohexane), m), 1.89-2.05 (2H β , m), 4.32-4.44 (1H α , m).

(b) Preparation of 3-cyclohexyl-2S-(furan-2-ylmethylsulfanyl)propionic acid (Compound (41), Scheme 9)

(R)- α -bromocyclohexanepropionic (0.37g, 1.58mmol) and furan-2-yl methanethiol (0.18g, 1.58mmol) were dissolved in dimethylformamide (10ml) and purged with nitrogen for 10minutes. The solution was cooled to 0°C then triethylamine (0.22ml, 1.58mmol) was added drop-wise over 1 minute. The mixture was stirred at 0°C for 30minutes then at ambient temperature for 16hours. The solvent was removed *in vacuo*, and the residue purified by chromatography over gel silica using methanol : dichloromethane 1:100 as eluent. Appropriate fractions were combined and the solvents removed *in vacuo* to give 3-cyclohexyl-2S-(furan-2-ylmethylsulfanyl)propionic acid (41) as a light brown oil, yield 142mg, (33%). Analytical HPLC peak Rt = 18.68mins. TLC (single spot, Rf = 0.45, 10% methanol in dichloromethane), HPLC-MS (single main peak with Rt = 9.53mins, 291.0 [M + Na]⁺).

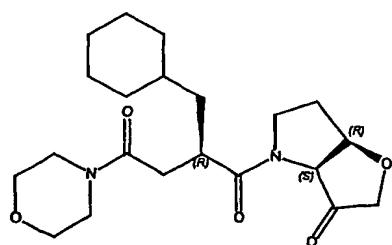
15

δ _H (400MHz, CDCl₃ at 298K), 0.68-0.89 (2H, CH₂(cyclohexane), m), 0.97-1.77 (11H, CH(cyclohexane), CH₂(cyclohexane), m), 3.21-3.32 (1H α , t, J = 7.79 Hz), 3.69-3.79 (1H, CH₂S, d, J = 14.79 Hz), 3.84-3.94 (1H, CH₂S, d, J = 14.8 Hz), 6.15-6.28 (2H, furan H-3 and H-4, d, J = 27.34 Hz), 7.30 (1H, furan H-5, s).

20

Compound (41) was coupled under standard conditions to loaded building block-linker construct (22). The intermediate loaded thioether (1.2 μ mole gear) was oxidised with m-chloroperbenzoic acid (5eq, 65% reagent, 1.6mg) in dichloromethane (200 μ L) for 5hrs, followed by standard washing and then cleaved to provide EXAMPLE 76.

EXAMPLE 77. (3aS, 6aR) 2R-Cyclohexylmethyl-4-morpholin-4-yl-1-(3-oxo-hexa hydrofuro[3,2-b]pyrrol-4-yl)butane-1,4-dione



HPLC-MS 393.1 $[M + H]^+$, 807.3 $[2M + Na]^+$.

(a) Preparation of 2*R*-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid methyl

5 ester.

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.HCl (1.12g, 5.69mmol) then 1-hydroxybenzotriazole monohydrate (0.87g, 5.69mmol) were added to a stirred solution of 2*R*-(cyclohexylmethyl)succinic acid 1-methyl ester (compound (35), 1.0g, 4.38mmol) in dimethylformamide (10ml) at 0°C under argon. The mixture was stirred for 25minutes then morpholine (0.7 ml, 8.76mmol) was added drop-wise over 1minute and stirring continued at ambient temperature for 16hours. The product was extracted into ethyl acetate (200ml) then washed with 1.0M hydrochloric acid (3 x 100ml), saturated aqueous sodium hydrogen carbonate solution (3 x 100ml), water (100ml), then saturated aqueous sodium chloride solution (100ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to give 2*R*-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid methyl ester as an off-white solid, yield 1.22g, (94%). HPLC-MS (single peak with R_t = 7.91mins, 298.1 $[M + H]^+$, 617.3 $[2M + Na]^+$).

20 (b) Preparation of 2*R*-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (Compound (36), Scheme 7).

A solution of lithium hydroxide monohydrate (0.51g, 12.18mmol) in water (27ml) was added a stirred solution of 2*R*-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid methyl ester (1.21g, 4.06mmol) in tetrahydrofuran (55ml) and methanol (27ml) at 0°C. The mixture was stirred at ambient temperature for 1 hours then diluted with water (100ml). The aqueous layer was extracted with diethyl ether (2 x 50ml) which was discarded, then acidified to pH = 1-2 with 1M hydrochloric acid. The product was extracted into dichloromethane (3 x 50ml), then the combined ethereal layers washed with water (2 x 50ml), saturated aqueous sodium chloride solution (2 x 50ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a residue. The residue was purified by chromatography over silica gel eluting with a gradient of

methanol : dichloromethane 1:100 → 3:100. Appropriate fractions were combined and the solvents removed *in vacuo* was to give 2*R*-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyric acid (36) as a white solid, yield 0.82 g, (71%). HPLC-MS (single peak with Rt = 6.769mins, 284.2 [M + H]⁺, 589.2 [2M + Na]⁺).

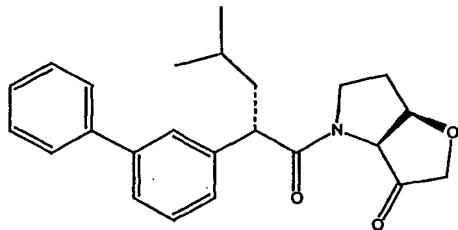
5

δ_H (400MHz, CDCl₃ at 298K), 0.77-0.90 (2H, CH₂(cyclohexane), m), 1.05-1.40 (4H, CH₂(cyclohexane), m), 1.50-1.90 (7H, CH(cyclohexane), CH₂(cyclohexane), m), 2.30-2.44 (2H β , m), 2.64-2.77 (1H α , m), 2.96-3.10 (1H, OH, brs), 3.40-3.78 (8H, CH₂OCH₂ and CH₂NCH₂, m).

10

Compound (36) was coupled under standard conditions to loaded building block-linker construct (22), then cleaved to provide EXAMPLE 77.

EXAMPLE 78. (3*aS*, 6*aR*) 4-(2-Biphenyl-3-yl-4-methylpentanoyl)tetrahydrofuro[3,2-*b*]pyrrol-3-one



HPLC Rt = 19.09-20.76mins (>90%), HPLC-MS 378.4 [M + H]⁺

20 (a) Preparation of Biphenyl-3-yl-acetic acid methyl ester (Compound (38), Scheme 8)

Concentrated sulphuric acid (588 μ L) was added to a solution of 3-bromophenyl acetic acid (10g, 46.5mmol) in methanol (100mL). The mixture was refluxed for 1.5h and then cooled to ambient temperature and evaporated under reduced pressure

25 to afford a residue. The residue was redissolved in diethyl ether (500mL), washed with water (2 x 100mL), brine (100mL), dried (MgSO₄) and then evaporated under reduced pressure to afford 3-bromophenyl acetic acid methyl ester (10.65g). The 3-bromophenyl acetic acid methyl ester was dissolved in toluene (117mL) then phenyl

boronic acid (6.8g, 55.69mmol) added, followed by a aqueous solution of sodium carbonate (93mL, 2M) and tetrakis(triphenylphosphine)palladium (1.6g, 1.41mmol). The mixture was stirred overnight then cooled to ambient temperature and an aqueous solution of saturated ammonium chloride (100mL) added. The mixture was 5 extracted with ethyl acetate (2 x 200mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue. Flash chromatography of the residue over silica (200g) using ethyl acetate : heptane (3 : 48) as the eluent gave biphenyl-3-yl acetic acid methyl ester, yield 10.5g, (99 %), TLC (single UV spot, R_f = 0.24, 10% ethyl acetate in heptane), analytical HPLC R_t = 19.55 min, HPLC-MS (single main UV 10 peak with R_t = 9.35 min, 227.1 $[\text{M} + \text{H}]^+$).

δ_{H} (400MHz, CDCl_3 at 298K) 3.76 (2H, s, $\text{CH}_2\text{CO}_2\text{CH}_3$), 3.77 (3H, s, OCH_3), 7.34-7.66 (9H, m, biphenyl-3-yl).

15 (b) Preparation of Biphenyl-3-yl-acetic acid

Water (39mL), followed by lithium hydroxide monohydrate (4.2g, 101.5mmol) were added to a solution of biphenyl-3-yl acetic acid methyl ester (11.43g, 50.57mmol) in methanol (265mL). The mixture was stirred at ambient temperature for 2h then the 20 organics were removed under reduced pressure. The mixture was acidified with dilute hydrochloric acid (1M, 80mL), extracted with chloroform (2 x 100mL), dried (MgSO_4) and evaporated under reduced pressure to afford biphenyl-3-yl acetic acid as a white solid, yield 10.6g, (99%), analytical HPLC R_t = 16.565 min, HPLC-MS (single main UV peak with R_t = 7.91min, 213.1 $[\text{M} + \text{H}]^+$).

25

δ_{H} (400MHz, CDCl_3 at 298K) 3.77 (2H, s, $\text{CH}_2\text{CO}_2\text{CH}_3$), 7.28-7.52 (9H, m, biphenyl-3-yl).

30 (c) Preparation of 2*RS*-Biphenyl-3-yl-4-methylpent-4-enoic acid

A solution of biphenyl-3-yl acetic acid (7.0g, 33mmol) in anhydrous tetrahydrofuran (84mL) was added dropwise to a solution of lithium diisopropyl amide (36.4mL, 2M

solution in hexanes) in anhydrous tetrahydrofuran (84mL) at -78 °C. The mixture was allowed to warm to 0 °C and stirred for 40 min. The mixture was then cooled to -78 °C and 3-bromo-2-methylpropene (4.97mL) rapidly added. The mixture was stirred for 1 h at -78 °C then water (28mL) added and the organics removed under reduced pressure. The mixture was then acidified with hydrochloric acid (6M, 14ml), extracted with ethyl acetate (3 x 100 ml), dried (MgSO₄) and evaporated under reduced pressure to afford a residue. Flash chromatography of the residue over silica (400g) using methanol : dichloromethane (3 : 97) as the eluent afforded impure 2-biphenyl-3-yl-4-methylpent-4-enoic acid (8.3 g). Flash chromatography over silica (400g) using methanol : dichloromethane (1.5 : 98.5) afforded pure 2-biphenyl-3-yl-4-methylpent-4-enoic acid, yield 5.27g, (60 %), TLC (single UV spot, R_f = 0.28, 5 % methanol in dichloromethane), analytical HPLC R_t = 19.99 min, HPLC-MS (single main UV peak with R_t = 9.57 min, 267.1 [M + H]⁺).

15 δ_H (400MHz, CDCl₃ at 298K), 1.765 (3H, s, CH₃), 2.53 (1H, dd, J = 6.6 and 14.7 Hz, 3-H₁), 2.91 (1H, dd, J = 8.9 and 14.7 Hz, 3-H₁), 3.92 (1H, dd, J = 6.6 and 8.9 Hz, 2-H), 4.79 (2H, d, J = 10.7 Hz, 5-H₂), 7.30-7.62 (9H, m, biphenyl-3-yl).

20 (d) Preparation of 2*RS*-Biphenyl-3-yl-4-methylpentanoic acid (Compound (39), Scheme 8)

Palladium on carbon (10%, 300mg) was added portionwise to a solution of 2*RS*-biphenyl-3-yl-4-methylpent-4-enoic acid (1g, 3.76mmol) in ethanol (40mL) at 0 °C. A hydrogen atmosphere was then introduced and the mixture allowed to warm to ambient temperature. The mixture was stirred for 18h, then the hydrogen atmosphere removed and the mixture filtered over Celite and the catalyst washed with ethanol (40mL). The combined organic filtrate was concentrated under reduced pressure to afford a residue, which was flash chromatographed over silica (150g) using methanol : dichloromethane (1 : 99) as the eluent to afford 2*RS*-biphenyl-3-yl-4-methylpentanoic acid, yield 980mg, (98%), TLC (single UV spot, R_f = 0.45, 5 % methanol in dichloromethane), analytical HPLC R_t = 20.92 min, HPLC-MS (single main UV peak with R_t = 10.15 min, 269.1 [M + H]⁺, 291.1 [M+Na]⁺).

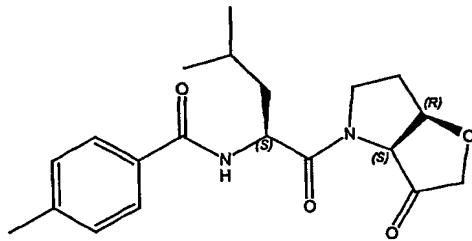
δ_H (400MHz, CDCl₃ at 298K), 0.93 (6H, d, J = 6.6 Hz, 2 x CH₃), 1.52-1.57 (1H, m, 4-H₁), 1.71-1.76 (1H, m, 3-H₁), 1.97-2.05 (1H, m, 3-H₁), 3.66 (1H, t, J = 7.8 Hz, 2-H₁), 7.32-7.60 (9H, m, biphenyl-3-yl).

5

Compound (39) was coupled under standard conditions to loaded building block-linker construct (22), then cleaved to provide EXAMPLE 78.

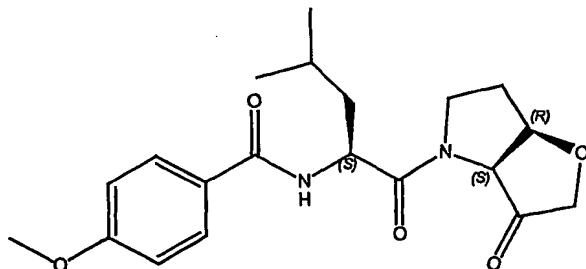
EXAMPLE 79. (3aS, 6aR) 4-Methyl-N-[3-methyl-1S-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide

10



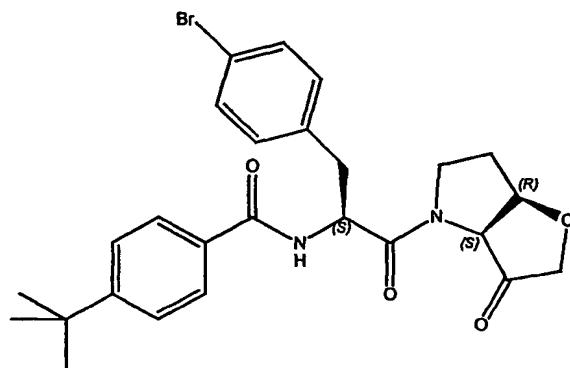
HPLC Rt = 13.74-14.85mins (> 90%), HPLC-MS 359.2 [M + H]⁺.

15 EXAMPLE 80. (3aS, 6aR) 4-Methoxy-N-[3-methyl-1S-(3-oxo-hexahydrofuro[3,2-*b*]pyrrole-4-carbonyl) butyl]benzamide



HPLC Rt = 12.95-13.87mins (> 90%), HPLC-MS 375.2 [M + H]⁺.

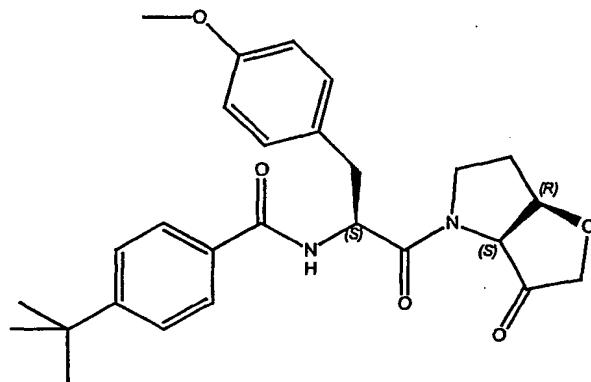
EXAMPLE 81. (3a*S*, 6a*R*) 4-*tert*-Butyl-N-[1*S*-(4-bromobenzyl)-2-oxo-2-(3-oxohexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 18.40-19.10mins (> 90%), HPLC-MS 513.2 / 515.2 [M + H]⁺.

5

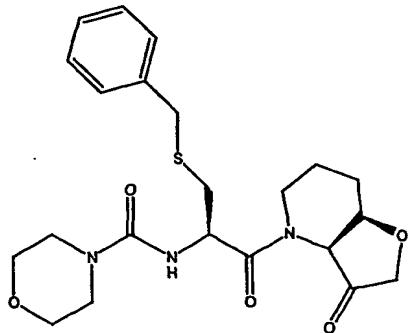
EXAMPLE 82. (3a*S*, 6a*R*) 4-*tert*-Butyl-N-[1*S*-(4-methoxybenzyl)-2-oxo-2-(3-oxohexahydrofuro[3,2-*b*]pyrrol-4-yl)ethyl]benzamide



HPLC Rt = 17.50-18.31mins (> 90%), HPLC-MS 465.2 [M + H]⁺.

10

EXAMPLE 83 (An example of general formula (II)). (3a*S*, 7a*R*) Morpholine-4-carboxylic acid [1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



The required bicyclic building block (3a*S*, 7a*R*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester was prepared in 8 steps as follows.

5 (1) Preparation of *Cis-rac*-(3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester.

Cis-rac-(3-hydroxy)piperidine-2-carboxylic acid (obtained by hydrogenation of commercially available 3-hydroxypicolinic acid, see Drummond, J. *et al*, *J. Med. Chem.*, 32, 2116-2128, 1989) (15.0g, 103.4mmole) was added to a vigorously stirred, ice-cooled solution of sodium carbonate (22.90g, 217.1mmole) in water (200mL). 1,4-Dioxan (100mL) was added providing a clear pale yellow solution. 9-Fluorenylmethyl chloroformate (27.52g, 108.4mmole) in 1,4-dioxan (100mL) was added over 1hr, then the ice-cooling removed and the mixture stirred at RT for an additional 1hr. Additional water (150mL) was added, the reaction mixture washed with chloroform (2 x 250mL) and the combined organic layers discarded. The aqueous phase was acidified with 1N HCl to ~ pH 2, providing a thick opaque mixture. The acidified aqueous mixture was extracted with chloroform (2 x 500mL) and the now clear aqueous phase discarded. The opaque combined chloroform layers were dried (Na_2SO_4), filtered and reduced in vacuo to provide a white foam, yield 30.2g (82.2mmole, 79.5%). TLC (Minor UV spot, R_f = 0.58, major UV spot R_f = 0.25, methanol : chloroform 1:4), analytical HPLC major peak R_t = 16.990mins, HPLC-MS (single major UV peak with R_t = 7.976mins, $368.0 [\text{M} + \text{H}]^+$, $390.0 [\text{M} + \text{Na}]^+$. Analysis by ^1H and ^{13}C NMR

showed the presence of cis and trans geometrical isomers around the 3° amide bond.

δ C (DMSO-d₆ at 298K); 23.29/23.57 (d, C_δ), 28.89 (d, C_γ), 40.19 (d, C_ε), 47.59 (u, Fmoc C-9), 59.11/59.43 (u, C_α), 67.34 (u, C_β), 67.75/67.87 (d, Fmoc CH₂), 121.13 (u, Fmoc C-4 and C-5), 126.90/127.02 (u, Fmoc C-1 and C-8), 128.11 (u, Fmoc C-2 and C-7), 128.68 (u, Fmoc C-3 and C-6), 141.73 (q, Fmoc C-4' and C-5'), 144.58/144.76 (q, Fmoc C-1' and C-8'), 155.71/156.23 (q, OCON), 172.37/172.63 (COOH).

10 (2) Preparation of *Cis-rac*-(3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

Cis-rac-(3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-yl methyl) ester (28.2g, 76.7mmole) was dissolved in toluene (200mL) in a Dean-Stark apparatus. Allyl alcohol (50mL) was added followed by *p*-toluenesulphonic acid hydrate (15.1g, 78.2mmole). The mixture was refluxed for 1hr, cooled and CHCl₃ (500mL) added. The organic layer was washed with NaHCO₃ (2 x 250mL), 0.1N HCl (250mL) and brine (250mL), then dried (Na₂SO₄). Filtration and reduction in vacuo gave a pale yellow mobile oil (35g). The crude oil was purified over silica gel (240g) eluting with a gradient of heptane : ethyl acetate 3:1 \rightarrow 1:1. Desired fractions were combined and reduced in vacuo to a colourless gum yield 20.4g (50.1mmole, 65.3%). TLC (single UV spot, R_f = 0.20, heptane : ethyl acetate 2:1), analytical HPLC R_t = 20.003mins, HPLC-MS (single main UV peak with R_t = 9.473mins, 408.1 [M + H]⁺, 430.1 [M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

δ H (CDCl₃ at 298K); 1.55 (2H_γ or 2H_δ, d, J 9.3), 1.81 (1H_γ or 1H_δ, d, J 3.2), 2.06 (1H_γ or 1H_δ, d, J 3.2), 2.78/2.92 (1H_ε, dbt), 3.55 (1H_β, dd, J 12.6, 9.2), 3.78 (OH, b), 3.95/4.11 (1H_ε, d, J 13), 4.31 (Fmoc H-9, m), 4.49 (Fmoc CH₂, m), 4.71 (2 x COOCH₂CH=CH₂, m), 4.99/5.17 (H_α, d, J 4.8), 5.31 (2 x COOCH₂CH=CH₂, m), 5.87 (1 x COOCH₂CH=CH₂, m), 7.37 (2H aromatic,

Fmoc H-2 and H-7), 7.47 (2H aromatic, Fmoc H-3 and H-6), 7.62 (2H aromatic, Fmoc H-1 and H-8), 7.83 (2H aromatic, Fmoc H-4 and H-5).
 δ C (CDCl₃ at 298K); 23.87/24.11 (d, C₈), 30.59 (d, C_γ), 41.26/41.56 (d, C_ε),
47.62 (u, Fmoc C-9), 58.29/59.54 (u, C_α), 66.44/66.54 (d,
5 COOCH₂CH=CH₂), 68.28 (d, Fmoc CH₂), 69.14/69.42 (u, C_β),
119.67/119.90 (d, COOCH₂CH=CH₂), 120.43 (u, Fmoc C-4 and C-5),
125.22/125.35 (u, Fmoc C-1 and C-8), 127.48 (u, Fmoc C-2 and C-7), 128.15
(u, Fmoc C-3 and C-6), 131.43/131.57 (u, COOCH₂CH=CH₂), 141.73 (q,
10 Fmoc C-4' and C-5'), 144.19/144.38 (q, Fmoc C-1' and C-8'), 155.67/156.27
(q, OCON), 171.56 (COOCH₂CH=CH₂).

(3) Enzymic Resolution of *Cis-rac*-(3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester to (2*R*, 3*S*) (3-hydroxy) pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester and (2*S*, 3*R*) (3-acetoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.
Cis-rac-(3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (19.6g, 48.1mmole), Lipase PS (25g, ex Amano Enzyme Inc.), vinyl acetate (300mL) and isopropyl ether (200mL) were stirred at 38°C. After 5 days, HPLC indicated equilibration of 2 peaks (52% : 48%, indicating 95% conversion) and the reaction mixture was filtered through celite (3cm x 10cm bed). The celite bed was washed with chloroform (3 x 250mL) and the combined organic filtrate reduced in vacuo to a viscous tan oil (23.0g). The crude oil was purified over silica gel (300g) eluting with a gradient of heptane : ethyl acetate 3:1 → 1:2. Two major fractions were identified and reduced in vacuo.

Product 1. (2*S*, 3*R*) (3-acetoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.
30 A viscous very pale yellow oil, yield 9.5g (21.1mmole, 43.9%). TLC (single UV spot, R_f = 0.40, heptane : ethyl acetate 2:1), analytical HPLC R_t = 22.633mins, HPLC-MS (single main UV peak with R_t = 10.714mins, 450.1

[M + H]⁺, 472.1 [M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

5 ¹H (CDCl₃ at 298K); 1.25-1.32/1.52-1.70/1.72-2.00 (2H_γ + 2H_δ, bm), 2.05-2.15 (OCOCH₃, bs), 3.35-3.58 (1H_ε, m), 3.98-4.10/4.18-4.22 (1H_ε, dd), 4.24-4.31 (Fmoc H-9, m), 4.32-4.52 (Fmoc CH₂, m), 4.60-4.82 (2 x COOCH₂CH=CH₂, m), 4.92-4.99 (H_β, m), 5.22-5.32 (H_α, m), 5.28-5.32/5.34-5.41 (2 x COOCH₂CH=CH₂, dd, *J*17.2), 5.89-6.00 (1 x COOCH₂CH=CH₂, m), 7.30-7.37 (2H aromatic, Fmoc H-2 and H-7), 7.38-7.46 (2H aromatic, Fmoc H-3 and H-6), 7.59-7.76 (2H aromatic, Fmoc H-1 and H-8), 7.78-7.80 (2H aromatic, Fmoc H-4 and H-5, d, *J*7.5).

10 ¹³C (CDCl₃ at 298K); 21.22 (u, OCOCH₃), 23.01 (d, C_δ), 25.54 (d, C_γ), 40.51/40.88 (d, C_ε), 47.44 (u, Fmoc C-9), 55.55 (u, C_α), 66.08 (d, COOCH₂CH=CH₂), 68.30/68.65 (d, Fmoc CH₂), 69.21/69.59 (u, C_β), 118.94/119.22 (d, COOCH₂CH=CH₂), 120.31 (u, Fmoc C-4 and C-5), 125.34/125.49 (u, Fmoc C-1 and C-8), 127.43 (u, Fmoc C-2 and C-7), 128.04 (u, Fmoc C-3 and C-6), 131.93 (u, COOCH₂CH=CH₂), 141.61 (q, Fmoc C-4' and C-5'), 144.15 (q, Fmoc C-1' and C-8'), 155.50/156.36 (q, OCON), 169.42/169.91/170.37 (COOCH₂CH=CH₂ + OCOCH₃).

20

Product 2. (2*R*, 3*S*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

25 A white crystalline solid, yield 9.05g (22.2mmole, 46.1%). TLC (single UV spot, R_f = 0.20, heptane : ethyl acetate 2:1), analytical HPLC Rt = 19.970mins, HPLC-MS (single main UV peak with Rt = 9.450mins, 408.1 [M + H]⁺, 430.1 [M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

30 ¹H (CDCl₃ at 298K); 1.47-1.61 (1H_γ + 1H_δ, m), 1.71-1.81 (1H_δ, b), 2.02-2.11 (1H_γ, b), 2.71-2.81/2.84-2.94 (1H_ε, dt), 3.54-3.59 (H_β, m), 3.70-3.82 (OH, b), 3.93-3.96/4.10-4.16/4.11 (1H_ε, d, *J*10), 4.24-4.31 (Fmoc H-9, m), 4.40-4.56 (Fmoc CH₂, m), 4.61-4.78 (2 x COOCH₂CH=CH₂, m), 4.98/5.18 (H_α, d, *J*5.0), 5.25-5.37 (2 x COOCH₂CH=CH₂, m), 5.86-5.96 (1 x

COOCH₂CH=CH₂, m), 7.30-7.34 (2H aromatic, Fmoc H-2 and H-7), 7.41-7.48 (2H aromatic, Fmoc H-3 and H-6), 7.53-7.62 (2H aromatic, Fmoc H-1 and H-8), 7.79-7.81 (2H aromatic, Fmoc H-4 and H-5).

5 δ C (CDCl₃ at 298K); 23.87/24.12 (d, C_δ), 30.60 (d, C_γ), 41.27/41.57 (d, C_ε), 47.62 (u, Fmoc C-9), 58.29/59.54 (u, C_α), 66.44/66.54 (d, COOCH₂CH=CH₂), 68.28 (d, Fmoc CH₂), 69.15/69.42 (u, C_β), 119.67/119.91 (d, COOCH₂CH=CH₂), 120.42 (u, Fmoc C-4 and C-5), 125.22/125.35 (u, Fmoc C-1 and C-8), 127.48 (u, Fmoc C-2 and C-7), 128.15 (u, Fmoc C-3 and C-6), 131.42/131.57 (u, COOCH₂CH=CH₂), 141.73 (q, Fmoc C-4' and C-5'), 144.12/144.37 (q, Fmoc C-1' and C-8'), 155.67/156.26 (q, OCON), 171.57 (COOCH₂CH=CH₂).

10

(4) Preparation of (2*S*, 3*R*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

15 (2*S*, 3*R*) (3-acetoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (4.5g, 10mmole) was dissolved in allyl alcohol (50mL), cH₂SO₄ (200 μ L) added and heated to reflux for 24hrs. The mixture was cooled, EtOAc (250mL) added and washed with NaHCO₃ (250mL), brine (250mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a tan oil (4.2g). The crude oil was purified over silica gel (170g) eluting with a gradient of heptane : ethyl acetate 3:1 \rightarrow 1:1. Desired fractions were combined and reduced in vacuo to a white crystalline solid, yield 3.0g (7.37mmole, 73.7%). TLC (single UV spot, R_f = 0.20, heptane : ethyl acetate 2:1), analytical HPLC Rt = 19.474mins, HPLC-MS (single main UV peak with Rt = 9.507mins, 408.2 [M + H]⁺, 430.2 [M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

20

25

30 δ H (CDCl₃ at 298K); 1.46-1.59 (1H_γ + 1H_δ, m), 1.74-1.81 (1H_δ, b), 2.01-2.10 (1H_γ, b), 2.70-2.82/2.88-2.99 (1H_ε, dt), 3.49-3.62 (H_β, m), 3.70-3.80 (OH, b), 3.90-3.94/4.09-4.14 (1H_ε, dd), 4.26-4.32 (Fmoc H-9, m), 4.41-4.58 (Fmoc CH₂, m), 4.60-4.80 (2 x COOCH₂CH=CH₂, m), 4.96-4.98/5.17-5.18 (H_α, dd, J4.8), 5.25-5.42 (2 x COOCH₂CH=CH₂, m), 5.82-5.97 (1 x

COOCH₂CH=CH₂, m), 7.30-7.38 (2H aromatic, Fmoc H-2 and H-7), 7.42-7.48 (2H aromatic, Fmoc H-3 and H-6), 7.55-7.63 (2H aromatic, Fmoc H-1 and H-8), 7.79-7.84 (2H aromatic, Fmoc H-4 and H-5).

¹³C (CDCl₃ at 298K); 23.86/24.12 (d, C₈), 30.62 (d, C_γ), 41.28/41.57 (d, C_ε),
5 47.62 (u, Fmoc C-9), 58.29/59.54 (u, C_α), 66.43/66.54 (d, COOCH₂CH=CH₂), 68.27 (d, Fmoc CH₂), 69.15/69.43 (u, C_β),
119.69/119.91 (d, COOCH₂CH=CH₂), 120.42 (u, Fmoc C-4 and C-5),
125.22/125.35 (u, Fmoc C-1 and C-8), 127.47 (u, Fmoc C-2 and C-7), 128.14
10 (u, Fmoc C-3 and C-6), 131.43/131.57 (u, COOCH₂CH=CH₂), 141.73 (q, Fmoc C-4' and C-5'), 144.12/144.37 (q, Fmoc C-1' and C-8'), 155.67/156.26
(q, OCON), 171.57 (COOCH₂CH=CH₂).

(5) Preparation of (2*S*, 3*R*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

15 (2*S*, 3*R*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (1.75g, 4.30mmole) was dissolved in dry dichloromethane (20mL) in a 50mL glass pressure tube and cooled to -78°C. Isobutylene gas (~10mL) was condensed into the solution and cH₂SO₄ (100μL) added. A stirrer bar was added, the tube was sealed, the cooling removed and stirred at RT for 72hr. The sealed tube was cooled to -78°C, N-methylmorpholine (200μL, 1eq w.r.t. cH₂SO₄) and allowed to warm to RT, unsealed, with stirring over 2hr. Dichloromethane (75mL) was added and the organics washed with NaHCO₃ (75mL), then brine (75mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a pale tan oil (1.91g).
20 The crude oil was purified over silica gel (100g) eluting with a gradient of heptane : ethyl acetate 5:1 → 3:1. Desired fractions were combined and reduced in vacuo to a thick clear oil yield 1.59g (3.43mmole, 79.8%). TLC (single UV spot, R_f = 0.50, heptane : ethyl acetate 2:1), analytical HPLC R_t = 24.123mins, HPLC-MS (single main UV peak with R_t = 11.91mins, 408.2 [M + H-Bu⁴]⁺, 486.3 [M + Na]⁺, 949.5 [2M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.
25
30

5 δ H (CDCl₃ at 298K); 1.23 (9 x C(CH₃)₃, s), 1.46-1.98 (2H_γ + 2H_δ, m), 3.37-3.45/3.46-3.57 (1H_ε, dt), 3.61-3.72 (H_β, b), 3.90-3.99/4.02-4.10 (1H_ε, dd), 4.20-4.72 (Fmoc H-9 + Fmoc CH₂ + 2 x COOCH₂CH=CH₂, bm), 4.89/5.01 (H_α, dd, J6.3), 5.24 (1 x COOCH₂CH=CH₂, d, J10.5), 5.38 (1 x COOCH₂CH=CH₂, d), 5.88-5.99 (1 x COOCH₂CH=CH₂, m), 7.29-7.36 (2H aromatic, Fmoc H-2 and H-7), 7.38-7.47 (2H aromatic, Fmoc H-3 and H-6), 7.56-7.69 (2H aromatic, Fmoc H-1 and H-8), 7.76-7.81 (2H aromatic, Fmoc H-4 and H-5).

10 δ C (CDCl₃ at 298K); 23.69/23.99 (d, C_δ), 28.38/28.65 (u, C(CH₃)₃), 28.75 (d, C_γ), 40.40/40.72 (d, C_ε), 47.61 (u, Fmoc C-9), 58.36/58.47 (u, C_α), 65.67 (d, COOCH₂CH=CH₂), 67.82 (u, C_β), 67.99/68.13 (d, Fmoc CH₂), 74.97 (q, C(CH₃)₃), 118.44/118.57 (d, COOCH₂CH=CH₂), 120.40 (u, Fmoc C-4 and C-5), 125.39/125.48 (u, Fmoc C-1 and C-8), 127.46 (u, Fmoc C-2 and C-7), 128.10 (u, Fmoc C-3 and C-6), 132.49 (u, COOCH₂CH=CH₂), 141.71 (q, Fmoc C-4' and C-5'), 144.14/144.30 (q, Fmoc C-1' and C-8'), 155.44/157.00 (q, OCON), 170.43/171.05 (COOCH₂CH=CH₂).

15

(6) Preparation of (2S, 3R) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester.

20 (2S,3R) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (1.52g, 3.29mmole) was dissolved in dry dichloromethane (25mL) with stirring. Tetrakis(triphenylphosphine) palladium (0) (76mg, 0.066mmole, 0.02eq) was added, followed by phenyltrihydrosilane (0.71g, 0.622mL, 6.58mmole, 2eq). After 1hr, dichloromethane (150mL) was added and the organics washed with 0.01N HCl (150mL), brine (150mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a dark grey solid (2.05g). The crude solid was purified over silica gel (75g) eluting with a gradient of heptane : ethyl acetate 2:1 → 1:2. Desired fractions were combined and reduced in vacuo to a white crystalline yield 0.97g (2.29mmole, 69.6%). TLC (single UV spot, R_f = 0.25, heptane : ethyl acetate 1:1), analytical HPLC R_t = 21.310mins, HPLC-MS (single main UV peak with R_t = 10.254mins, 368.2 [M + H-Bu⁴]⁺, 446.2 [M

25

30

+ Na]⁺, 869.3 [2M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

¹H (CDCl₃ at 298K); 1.32/1.40 (9 x C(CH₃)₃, ds), 1.42-1.58 (1H_γ + 1H_δ, m), 1.72-1.80 (1H_δ, bm), 1.82-1.96 (1H_γ, bm), 2.76-2.82/2.90-2.97 (1H_ε, dt), 3.70-3.84 (H_β, b), 3.90-4.07 (1H_ε, dd), 4.22-4.32 (Fmoc H-9), 4.40-4.58 (Fmoc CH₂, bm), 4.59-4.61/5.02-5.04 (H_α, dd, J5.7), 7.29-7.36 (2H aromatic, Fmoc H-2 and H-7), 7.39-7.43 (2H aromatic, Fmoc H-3 and H-6), 7.53-7.67 (2H aromatic, Fmoc H-1 and H-8), 7.76-7.81 (2H aromatic, Fmoc H-4 and H-5), 10.90-11.10 (COOH, bs).

¹³C (CDCl₃ at 298K); 23.71/24.23 (d, C_δ), 28.21/28.28 (u, C(CH₃)₃), 30.58/30.72 (d, C_γ), 40.49/40.79 (d, C_ε), 47.58/47.63 (u, Fmoc C-9), 58.20/58.43 (u, C_α), 67.78/68.32 (u, C_β), 68.69/68.88 (d, Fmoc CH₂), 78.48/78.67 (q, C(CH₃)₃), 120.31 (u, Fmoc C-4 and C-5), 125.16/125.27/125.50/125.53 (u, Fmoc C-1 and C-8), 127.42/127.46/127.59 (u, Fmoc C-2 and C-7), 128.03/128.10 (u, Fmoc C-3 and C-6), 141.55/141.69/141.79 (q, Fmoc C-4' and C-5'), 144.06/144.12/144.38/144.48 (q, Fmoc C-1' and C-8'), 155.73/156.49 (q, OCON), 169.26/169.52 (COOH).

(7) Preparation of (2*S*, 3*R*) (3-*tert*-butoxy)-2-(2-diazoacetyl)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester.

(2*S*, 3*R*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester (830mg, 1.96mmole) was dissolved with stirring in dry dichloromethane (20mL). The reaction was flushed with nitrogen and cooled to -15°C. Isobutylchloroformate (296mg, 2.16mmole in dry dichloromethane (2.5mL) and N-methylmorpholine (397mg, 3.92mmole in dry dichloromethane (2.5mL) were added simultaneously in 0.5mL aliquots over 15mins. Etheral diazomethane (generated from diazald (2.5g, ~8mmole in diethyl ether (40mL)) onto sodium hydroxide (2.75g) in water (4.3mL) / ethanol (8.6mL) at 60°C). was added to the activated aminoacid solution and stirred at RT for 24hr. Acetic acid (~2mL) was added to quench the reaction, then *tert*-butylmethylether (100mL) was added, the organics washed with water (3 x 150mL), then dried (Na₂SO₄). The solvents were removed in

vacuo to give a thick yellow oil (1.02g). The crude oil was used for the next stage without purification. TLC (single main UV spot, $R_f = 0.40$, heptane : ethyl acetate 2:1), analytical HPLC $R_t = 18.887$ mins (50.8%) plus numerous minor peaks, HPLC-MS (2 main UV peaks with $R_t = 9.095$ mins, 364.2 [$M + H]^+$, 749.2 [$2M + Na]^+$ and $R_t = 10.856$ mins, 420.2 [$M + H - N_2]^+$, 470.2 [$M + Na]^+$, 917.3 [$2M + Na]^+$).

5 Note that upon HPLC-MS analysis, m/z 364.2 corresponds to the desired bicycle product (3aS, 7aR) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester.

10

(8) Cyclisation to (3aS, 7aR) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester.

15

A solution of lithium chloride (844mg, 20mmole) in water (5mL) and acetic acid (20mL) was added to (2*S*, 3*R*) (3-*tert*-butoxy)-2-(2-diazoacetyl)pyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester (1000mg, ~2mmole). Gas was evolved and the yellow oily solid dissolved over 1hr to give a virtually colourless solution. After 90mins, chloroform (150mL) was added and the organics washed with $NaHCO_3$ (2 x 150mL), brine (150mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give a pale yellow gum (920mg). The crude gum was purified over silica gel (135g) eluting with a gradient of heptane : ethyl acetate 3:1 \rightarrow 1:1. Desired fractions were combined and reduced in vacuo to a white crystalline solid, yield 370mg (1.02mmole, 51.9% from starting acid). TLC (single UV spot, $R_f = 0.25$, heptane : ethyl acetate 2:1), analytical HPLC $R_t = 18.734$ mins, HPLC-MS (single UV peak with $R_t = 9.051$ mins, 364.2 [$M + H]^+$, 386.2 [$M + Na]^+$). Analysis by 1H and ^{13}C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

20

25

30

35

1H ($CDCl_3$ at 298K); 1.29-1.49 (1*H_γ* + 1*H_δ*, m), 1.61-1.80 (1*H_δ*, bm), 2.06-2.19 (1*H_γ*, bm), 2.50-2.62/2.63-2.80 (1*H_ε*, m), 3.96 (1*H_ε*, b), 3.97 ($COCH_{2A}$, d, J 16.3), 4.15 (Fmoc H-9, bt), 4.25-4.34 (H $_{\beta}$, b), 4.36-4.60 (Fmoc CH_2 + $COCH_{2B}$, bm), 4.75-4.82/5.11-5.19 (H $_{\alpha}$, bd), 7.30-7.36 (2H aromatic, Fmoc H-2 and H-7), 7.41-7.49 (2H aromatic, Fmoc H-3 and H-6), 7.52-7.68

(2H aromatic, Fmoc H-1 and H-8), 7.75-7.85 (2H aromatic, Fmoc H-4 and H-5).

δ C (CDCl₃ at 298K); 21.75/22.04 (d, C₈), 26.60 (d, C₇), 41.40/41.66 (d, C₆), 47.59 (u, Fmoc C-9), 60.42 (u, C₉), 67.54 (d, Fmoc CH₂), 68.21/68.39 (d, COCH₂O), 72.61 (u, C₈), 120.39 (u, Fmoc C-4 and C-5), 125.43 (u, Fmoc C-1 and C-8), 127.51 (u, Fmoc C-2 and C-7), 128.14 (u, Fmoc C-3 and C-6), 141.73 (q, Fmoc C-4' and C-5'), 144.30 (q, Fmoc C-1' and C-8'), 155.79/156.35 (q, OCON), 211.10/211.4 (q, COCH₂O).

10 Following the general details from **Scheme 2**, the required bicyclic building block (3aS, 7aR) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester was converted to building block-linker construct as follows:

15 (3aS, 7aR) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (250mg, 0.689mmole) was dissolved in a mixture of ethanol (12.0mL) and water (1.75mL) containing sodium acetate trihydrate (141mg, 1.03mmole, 1.5eq). 4-[[(hydrazinocarbonyl)amino]methyl]cyclo hexanecarboxylic acid trifluoroacetate (227mg, 0.689mmole, 1.0eq, Murphy, A. M. *et al*, *J. Am. Chem. Soc.*, 114, 3156-3157, 1992) was added and the mixture refluxed for 4hrs.

20 Chloroform (150mL) was added and the organics washed with HCl (150mL, ~ pH3), dried (Na₂SO₄) and reduced in vacuo to provide crude building block-linker construct a clear viscous oil. Yield 350mg, analytical HPLC 2 peaks Rt = 17.101 (74.7%) and 18.547mins (25.3%) (cis / trans geometrical isomers), HPLC-MS (2 x UV peak with Rt = 8.037 and 8.972mins, 561.2 [M + H]⁺). Crude construct was used

25 directly for construct loading.

Following the general details from **Scheme 2**, the required building block-linker construct was attached to the solid phase providing loaded building block-linker construct as follows:

30 Building block-linker construct (0.595mmoles), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate (HBTU, 226.0mg, 0.596mmole), 1-

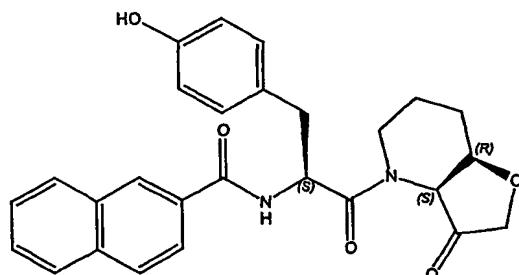
hydroxybenzotriazolehydrate and (HOBT, 92mg, 0.596mmole) were dissolved in dimethylformamide (3mL) and N-methylmorpholine (NMM, 131µL, 1.197mmole) added. After pre-activation for 5 minutes, free amine gears (160 x 1.2µmole) were added, followed by dimethylformamide (17.5mL) and left overnight. The spent 5 coupling solution was then added to free amine crowns (18 x 10µmole) and left overnight. Standard washing and analyses indicated quantitative loading in both cases.

Following the general details from Scheme 2, the required loaded building block-linker construct was elaborated on the solid phase as follows:

10 Loaded construct was elaborated to EXAMPLE 83 (3aS, 7aR) Morpholine-4-carboxylic acid [1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxohexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide by standard Fmoc deprotection and sequential coupling 15 with Fmoc-Cys(SBzl)-OH then morpholine-4-carbonylchloride. The crude example was cleaved and analysed (see general techniques). HPLC Rt = 15.59mins (>80%), HPLC-MS 449.2 [M + H]⁺.

20 The following examples (84 – 130) were prepared as detailed for EXAMPLE 83, coupling with the required reagents to provide the full length molecule.

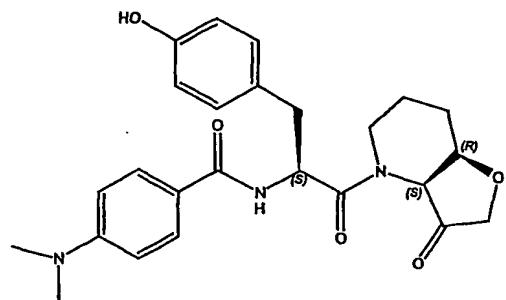
EXAMPLE 84. (3aS, 7aR) Naphthalene-2-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



25

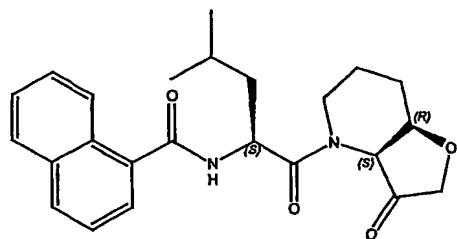
HPLC Rt = 15.79mins (> 80%), HPLC-MS 459.3 [M + H]⁺.

EXAMPLE 85. (3a*S*, 7a*R*) 4-Dimethylamino-N-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide



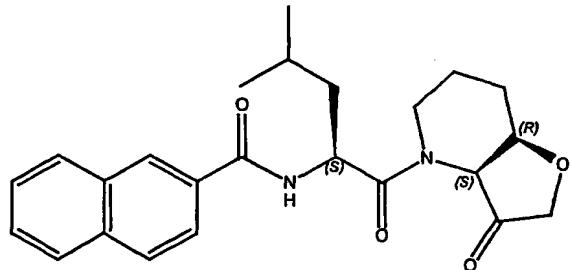
5 HPLC Rt = 10.98mins (> 80%), HPLC-MS 452.2 [M + H]⁺.

EXAMPLE 86. (3a*S*, 7a*R*) Naphthalene-1-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



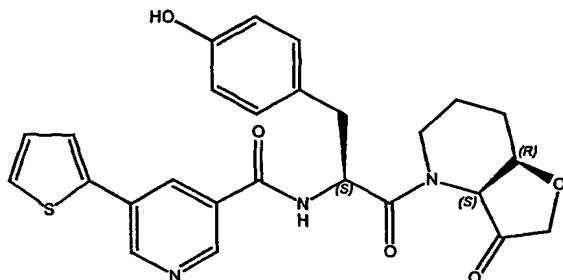
10 HPLC Rt = 17.71mins (> 80%), HPLC-MS 409.2 [M + H]⁺.

EXAMPLE 87. (3a*S*, 7a*R*) Naphthalene-2-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



15 HPLC Rt = 18.28mins (> 80%), HPLC-MS 409.2 [M + H]⁺.

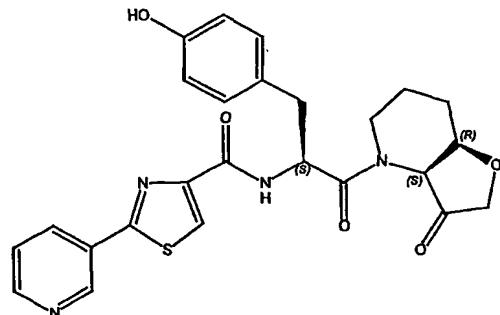
EXAMPLE 88. (3a*S*, 7a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-5-thiophen-2-ylnicotinamide



5

HPLC Rt = 13.16mins (> 80%), HPLC-MS 492.2 [M + H]⁺.

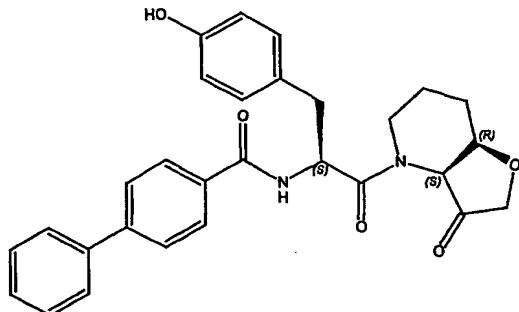
EXAMPLE 89. (3a*S*, 7a*R*) 2-Pyridin-3-ylthiazole-4-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



10

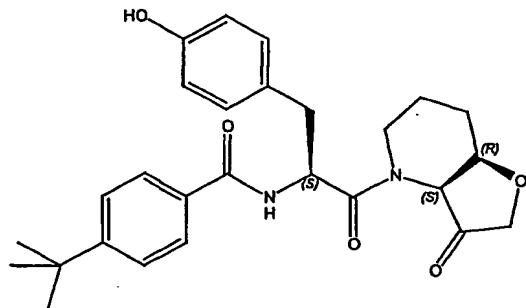
HPLC Rt = 10.45mins (> 80%), HPLC-MS 493.2 [M + H]⁺.

EXAMPLE 90. (3a*S*, 7a*R*) Biphenyl-4-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



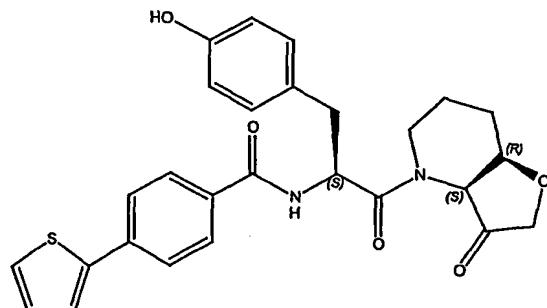
HPLC Rt = 17.38mins (> 80%), HPLC-MS 485.2 [M + H]⁺.

EXAMPLE 91. (3a*S*, 7a*R*) 4-*tert*-butyl-*N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-5-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide



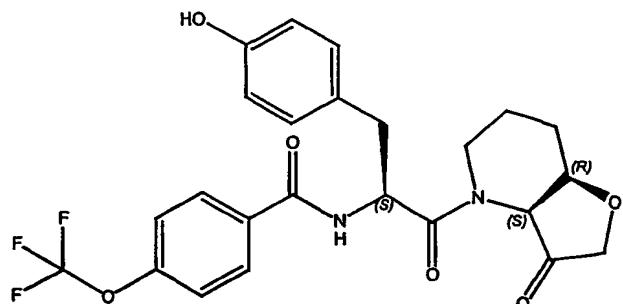
HPLC Rt = 17.90mins (> 80%), HPLC-MS 485.2 [M + H]⁺.

EXAMPLE 92. (3a*S*, 7a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-thiophen-2-ylbenzamide



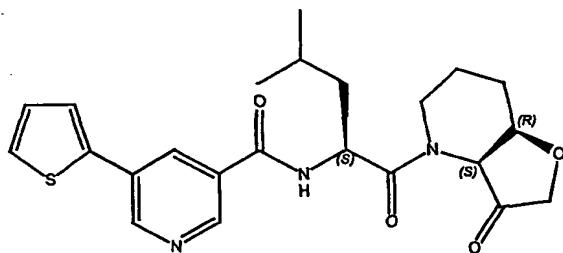
HPLC Rt = 17.00mins (> 80%), HPLC-MS 491.2 [M + H]⁺.

EXAMPLE 93. (3a*S*, 7a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]-4-trifluoromethoxybenzamide



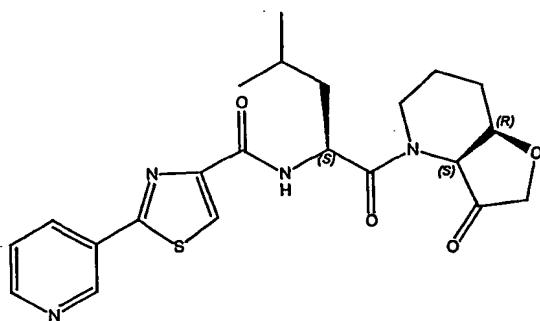
HPLC Rt = 17.07mins (> 80%), HPLC-MS 493.2 [M + H]⁺.

EXAMPLE 94. (3a*S*, 7a*R*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-5-thiophen-2-ylnicotinamide



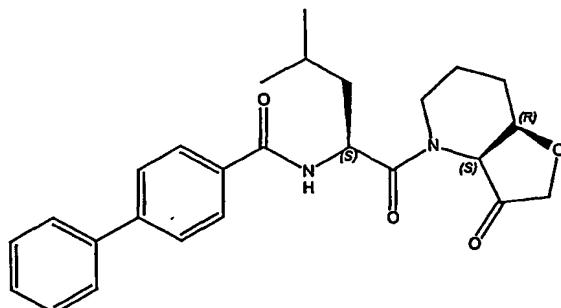
HPLC Rt = 15.82mins (> 80%), HPLC-MS 442.2 [M + H]⁺.

EXAMPLE 95. (3a*S*, 7a*R*) 2-Pyridin-3-ylthiazole-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



HPLC Rt = 12.55mins (> 80%), HPLC-MS 443.2 [M + H]⁺.

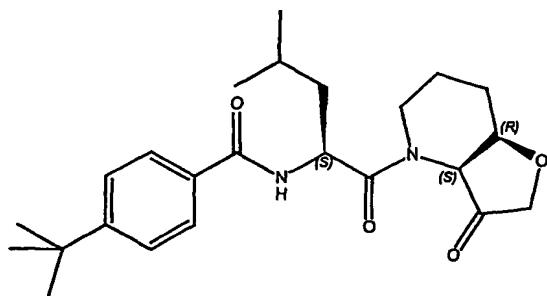
EXAMPLE 96. (3a*S*, 7a*R*) Biphenyl-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



-190-

HPLC Rt = 19.88mins (> 80%), HPLC-MS 435.2 [M + H]⁺.

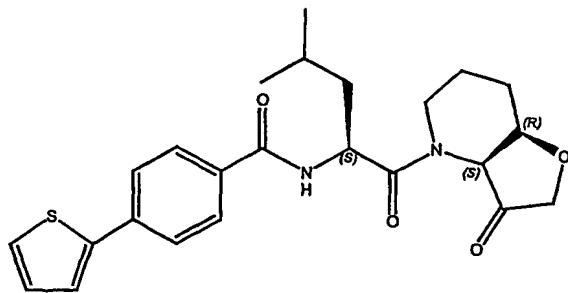
EXAMPLE 97. (3a*S*, 7a*R*) 4-*tert*-butyl-N-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide



5

HPLC Rt = 20.42mins (> 80%), HPLC-MS 415.2 [M + H]⁺.

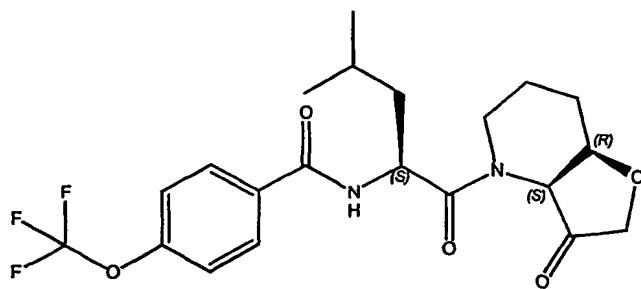
EXAMPLE 98. (3a*S*, 7a*R*) N-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-thiophen-2-ylbenzamide



10

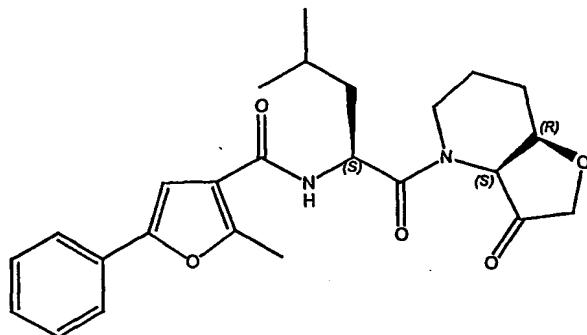
HPLC Rt = 19.60mins (> 80%), HPLC-MS 441.2 [M + H]⁺.

EXAMPLE 99. (3a*S*, 7a*R*) N-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]-4-trifluoromethoxybenzamide



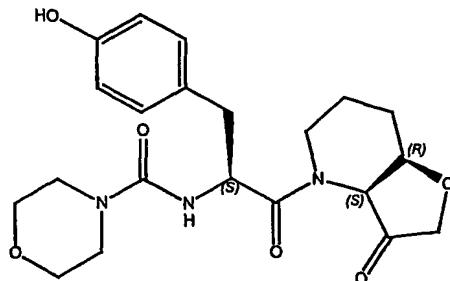
HPLC Rt = 19.66mins (> 80%), HPLC-MS 443.2 [M + H]⁺.

EXAMPLE 100. (3a*S*, 7a*R*) 2-Methyl-5-phenylfuran-3-carboxylic acid [3-methyl-
5 1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



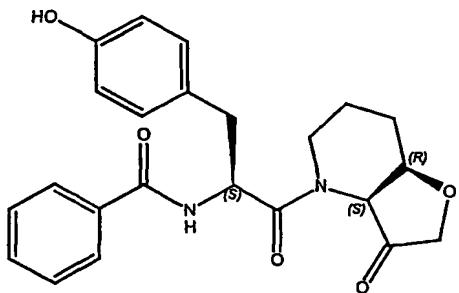
HPLC Rt = 20.48mins (> 80%), HPLC-MS 439.2 [M + H]⁺.

10 EXAMPLE 101. (3a*S*, 7a*R*) Morpholine-4-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-
oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



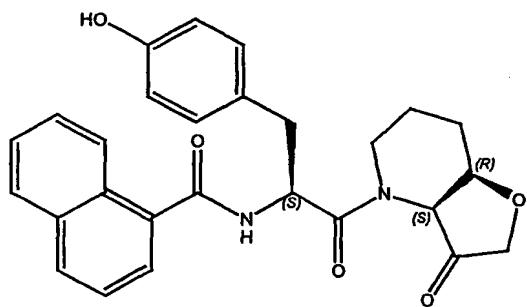
HPLC-MS 418.2 [M + H]⁺.

15 EXAMPLE 102. (3a*S*, 7a*R*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide



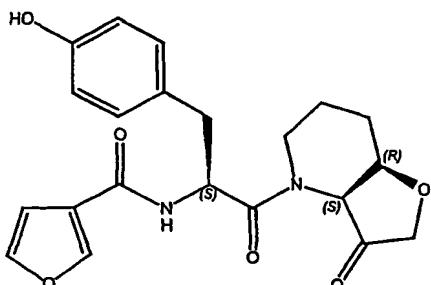
HPLC Rt = 12.71mins (>85%), HPLC-MS 409.2 [M + H]⁺.

5 EXAMPLE 103. (3aS, 7aR) Naphthalene-1-carboxylic acid [1S-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide



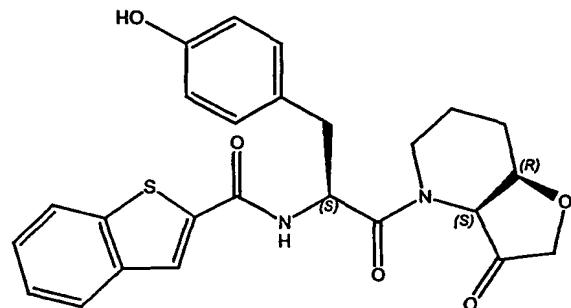
HPLC Rt = 14.88mins (>85%), HPLC-MS 459.2 [M + H]⁺.

10 EXAMPLE 104. (3aS, 7aR) Furan-3-carboxylic acid [1S-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-b]pyridin-4-yl)ethyl]amide



HPLC Rt = 11.14mins (>85%), HPLC-MS 399.2 [M + H]⁺.

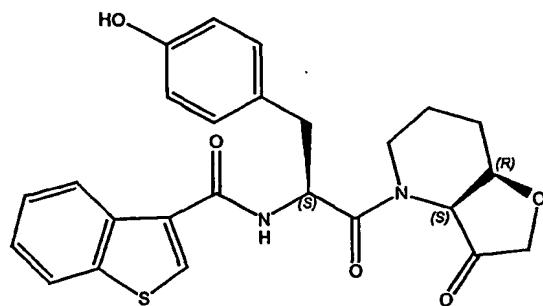
EXAMPLE 105. (3a*S*, 7a*R*) Benzo[*b*]thiophene-2-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



HPLC Rt = 15.99mins (>85%), HPLC-MS 465.2 [M + H]⁺.

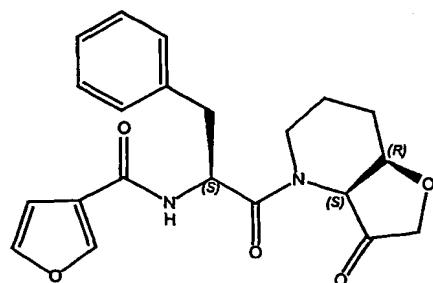
5

EXAMPLE 106. (3a*S*, 7a*R*) Benzo[*b*]thiophene-3-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



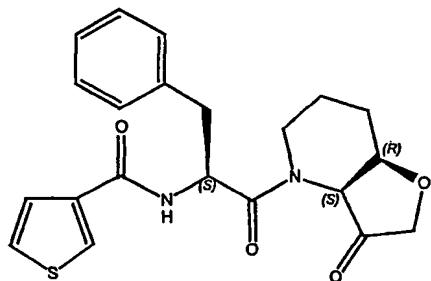
10 HPLC Rt = 15.58mins (>85%), HPLC-MS 465.2 [M + H]⁺, 951.3 [2M + Na]⁺.

EXAMPLE 107. (3a*S*, 7a*R*) Furan-3-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-oxohexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



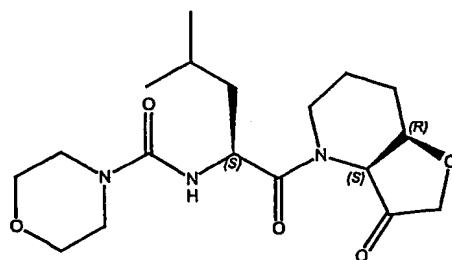
HPLC Rt = 14.44mins (>85%), HPLC-MS 383.2 [M + H]⁺.

EXAMPLE 108. (3a*S*, 7a*R*) Thiophene-3-carboxylic acid [1*S*-benzyl-2-oxo-2-(3-
5 oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



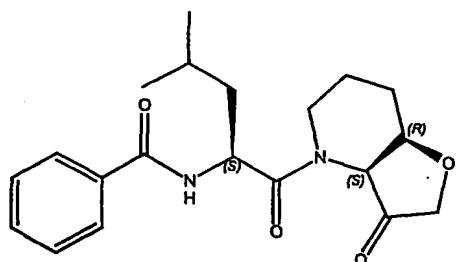
HPLC Rt = 15.34mins (>80%), HPLC-MS 399.2 [M + H]⁺.

EXAMPLE 109. (3a*S*, 7a*R*) Morpholine-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexa-
10 hydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



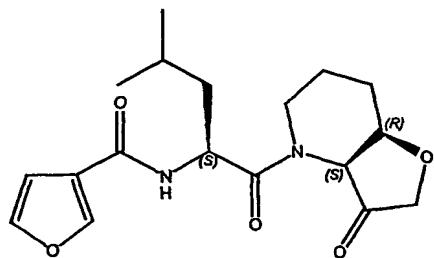
HPLC-MS 368.2 [M + H]⁺.

15 EXAMPLE 110. (3a*S*, 7a*R*) *N*-(3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-
carbonyl) butyl)benzamide



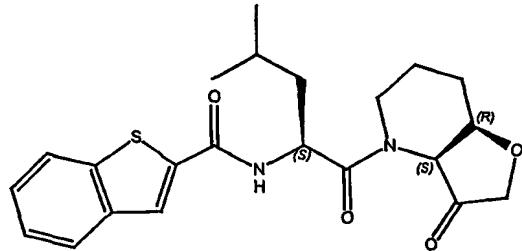
HPLC Rt = 15.42mins (>85%), HPLC-MS 359.2 [M + H]⁺.

EXAMPLE 111. (3a*S*, 7a*R*) Furan-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydro
5 furo[3,2-*b*]pyridine-4-carbonyl) butyl]amide



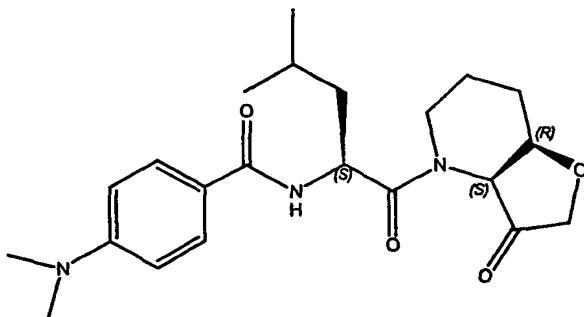
HPLC Rt = 13.74mins (>85%), HPLC-MS 349.2 [M + H]⁺.

EXAMPLE 112. (3a*S*, 7a*R*) Benzo[*b*]thiophene-2-carboxylic acid [3-methyl-1*S*-(3-
10 oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



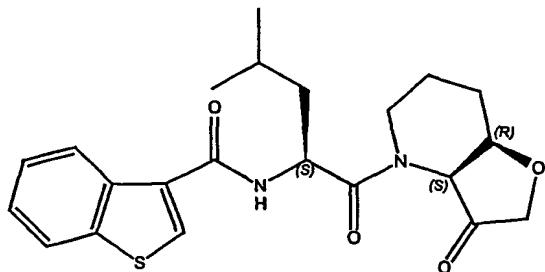
HPLC Rt = 18.52mins (>85%), HPLC-MS 415.2 [M + H]⁺, 851.3 [2M + Na]⁺.

EXAMPLE 113. (3a*S*, 7a*R*) 4-Dimethylamino-*N*-(3-methyl-1*S*-(3-oxo-hexahydro
15 furo[3,2-*b*]pyridine-4-carbonyl) butyl)benzamide



HPLC Rt = 13.55mins (>85%), HPLC-MS 402.2 [M + H]⁺.

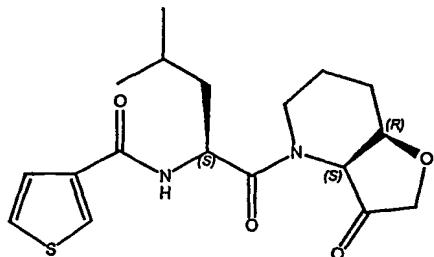
EXAMPLE 114. (3a*S*, 7a*R*) Benzo[*b*]thiophene-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



5

HPLC Rt = 18.26mins (>85%), HPLC-MS 415.2 [M + H]⁺.

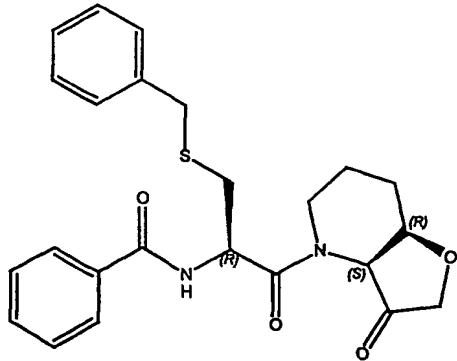
EXAMPLE 115. (3a*S*, 7a*R*) Thiophene-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



10

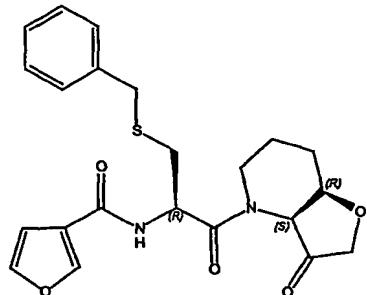
HPLC Rt = 14.80mins (>85%), HPLC-MS 365.2 [M + H]⁺.

EXAMPLE 116. (3a*S*, 7a*R*) *N*-[1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide



HPLC Rt = 17.78mins (>90%), HPLC-MS 439.2 [M + H]⁺, 899.3 [2M + Na]⁺.

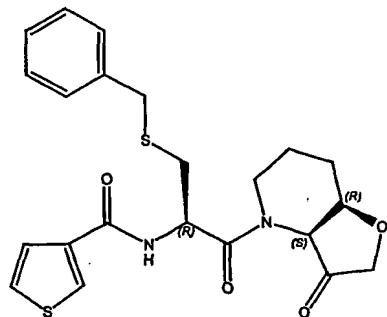
EXAMPLE 117. (3a*S*, 7a*R*) Furan-3-carboxylic acid-[1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



5

HPLC Rt = 16.41mins (>85%), HPLC-MS 429.2 [M + H]⁺, 451.2 [M + Na]⁺.

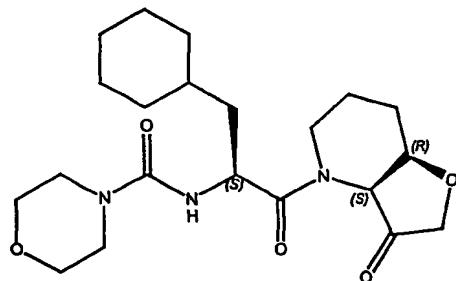
EXAMPLE 118. (3a*S*, 7a*R*) Thiophene-3-carboxylic acid-[1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



10

HPLC Rt = 17.23mins (>85%), HPLC-MS 445.2 [M + H]⁺, 911.2 [2M + Na]⁺.

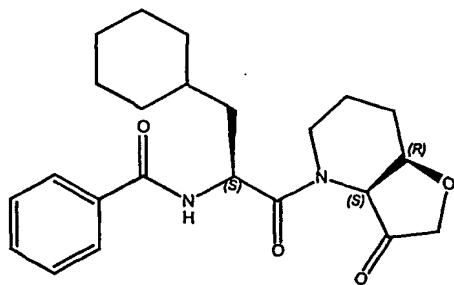
EXAMPLE 119. (3a*S*, 7a*R*) Morpholine-4-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-carbonyl)ethyl]amide



HPLC-MS 408.3 $[M + H]^+$, 430.3 $[M + Na]^+$.

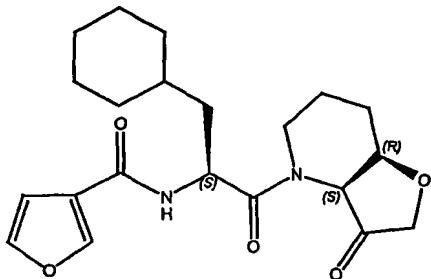
EXAMPLE 120. (3a*S*, 7a*R*) *N*-[1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro

5 [3,2-*b*]pyridin-4-yl)ethyl]benzamide



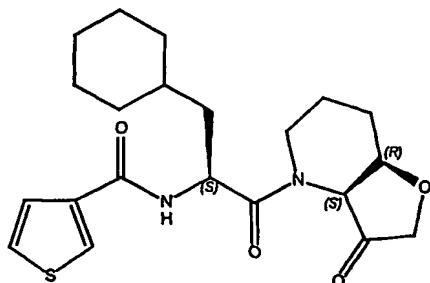
HPLC Rt = 18.47mins (>85%), HPLC-MS 399.2 $[M + H]^+$, 819.2 $[2M + Na]^+$.

10 EXAMPLE 121. (3a*S*, 7a*R*) Furan-3-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



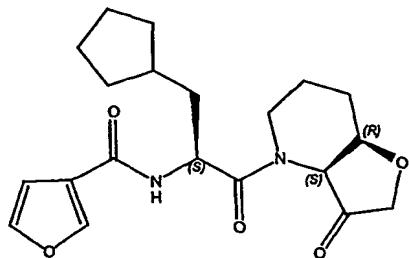
HPLC Rt = 17.12mins (>85%), HPLC-MS 389.2 $[M + H]^+$, 411.2 $[2M + Na]^+$.

15 EXAMPLE 122. (3a*S*, 7a*R*) Thiophene-3-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



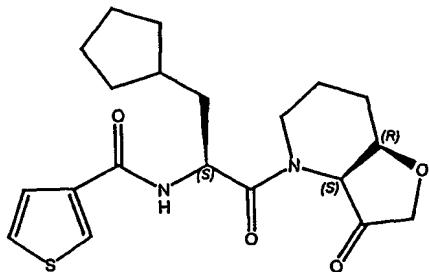
HPLC Rt = 17.95mins (>85%), HPLC-MS 405.2 [M + H]⁺, 831.2 [2M + Na]⁺.

EXAMPLE 123. (3a*S*, 7a*R*) Furan-3-carboxylic acid [1*S*-cyclopentylmethyl-2-oxo-2-
5 (3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



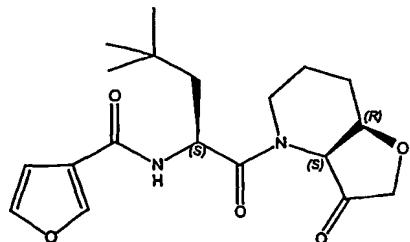
HPLC Rt = 15.80mins (>80%), HPLC-MS 375.2 [M + H]⁺, 771.3 [2M + Na]⁺.

EXAMPLE 124. (3a*S*, 7a*R*) Thiophene-3-carboxylic acid [1*S*-cyclopentylmethyl-2-
10 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



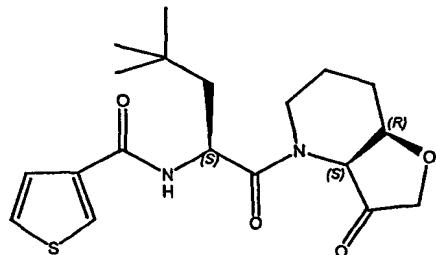
HPLC Rt = 16.72mins (>85%), HPLC-MS 391.1 [M + H]⁺, 803.3 [2M + Na]⁺.

EXAMPLE 125. (3a*S*, 7a*R*) Furan-3-carboxylic acid [3,3-dimethyl-1*S*-(3-oxo-hexa-
15 hydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



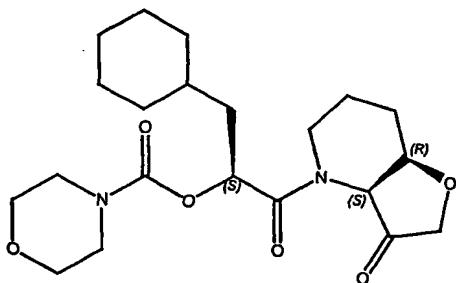
HPLC Rt = 15.06mins (>90%), HPLC-MS 363.2 [M + H]⁺, 747.4 [2M + Na]⁺.

EXAMPLE 126. (3a*S*, 7a*R*) Thiophene-3-carboxylic acid [3,3-dimethyl-1*S*-(3-oxo-5 hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



HPLC Rt = 15.75mins (>85%), HPLC-MS 379.2 [M + H]⁺, 779.3 [2M + Na]⁺.

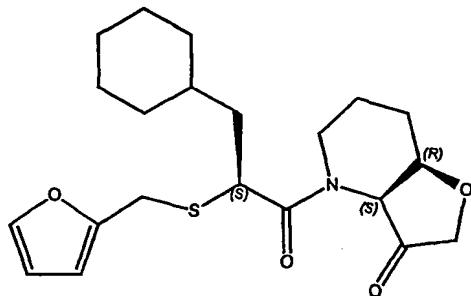
EXAMPLE 127. (3a*S*, 7a*R*) Morpholine-4-carboxylic acid 1*S*-cyclohexylmethyl-2-10 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl ester



HPLC-MS 409.2 [M + H]⁺, 839.5 [2M + Na]⁺.

As detailed for EXAMPLE 74, compound (33) was coupled under standard 15 conditions (following Fmoc removal) to the (3a*S*, 7a*R*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded building block-linker construct (22), then cleaved to provide EXAMPLE 127.

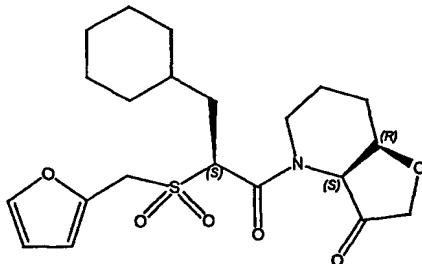
EXAMPLE 128. (2*S*, 3a*S*, 7a*R*) 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulfanyl)20 propionyl]hexahydrofuro[3,2-*b*]pyridin-3-one



HPLC-MS 392.1 [M + H]⁺, 805.2 [2M + Na]⁺.

As detailed for EXAMPLE 76, compound (41) was coupled under standard conditions (following Fmoc removal) to the (3a*S*, 7a*R*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded building block-linker construct (22), then cleaved to provide EXAMPLE 128.

EXAMPLE 129. (2*S*, 3*aS*, 7*aR*) 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulphonyl)propionyl]hexahydrofuro[3,2-*b*]pyridin-3-one



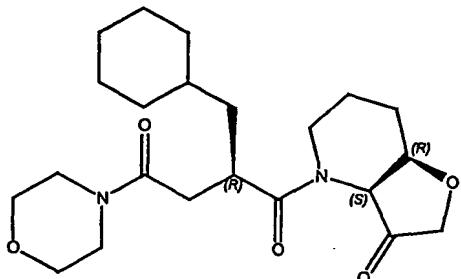
10

HPLC Rt = 19.015mins (>%), HPLC-MS 424.1 [M + H]⁺, 869.2 [2M + Na]⁺.

As detailed for EXAMPLE 76, compound (41) was coupled under standard conditions (following Fmoc removal) to the (3a*S*, 7a*R*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded building block-linker construct (22). The intermediate loaded thioether (1.2μmole gear) was oxidised with m-chloroperbenzoic acid (5eq, 65% reagent, 1.6mg) in dichloromethane (200μL) for 5hrs, followed by standard washing and then cleaved to provide EXAMPLE 129.

20

EXAMPLE 130. (3a*S*, 7a*R*) 2*R*-Cyclohexylmethyl-4-morpholin-4-yl-1-(3-oxo-hexa hydrofuro[3,2-*b*] pyridin-4-yl)butane-1,4-dione

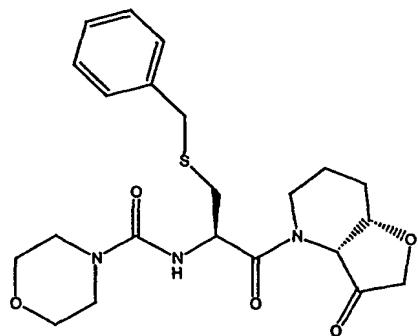


HPLC-MS 407.1 [M + H]⁺, 833.3 [2M + Na]⁺.

5

As detailed for EXAMPLE 77, compound (36) was coupled under standard conditions (following Fmoc removal) to the (3a*S*, 7a*R*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded building block-linker construct (22), then cleaved to provide EXAMPLE 130.

10 EXAMPLE 131 (An example of general formula (II)). (3a*R*, 7a*S*) Morpholine-4-carboxylic acid [1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxohexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



15 The required bicyclic building block (3a*R*, 7a*S*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester was prepared in a further 4 steps from (2*R*, 3*S*) (3-hydroxy) pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9*H*-fluoren-9-ylmethyl) ester as follows.

(1) Preparation of (*2R, 3S*) (*3-tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

(*2R, 3S*) (*3*-hydroxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (1.75g, 4.30mmole) was dissolved in dry dichloromethane (20mL) in a 50mL glass pressure tube and cooled to -78°C. Isobutylene gas (~10mL) was condensed into the solution and CH_2SO_4 (100 μL) added. A stirrer bar was added, the tube was sealed, the cooling removed and stirred at RT for 72hr. The sealed tube was cooled to -78°C, N-methylmorpholine (200 μL , 1eq w.r.t. CH_2SO_4) and allowed to warm to RT, unsealed, with stirring over 2hr. Dichloromethane (75mL) was added and the organics washed with NaHCO_3 (75mL), then brine (75mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give a pale tan oil (1.93g). The crude oil was purified over silica gel (100g) eluting with a gradient of heptane : ethyl acetate 5:1 \rightarrow 3:1. Desired fractions were combined and reduced in vacuo to a thick clear oil yield 1.48g (3.19mmole, 74.3%). TLC (single UV spot, R_f = 0.50, heptane : ethyl acetate 2:1), analytical HPLC R_t = 24.083mins, HPLC-MS (single main UV peak with R_t = 11.996mins, 408.2 [$\text{M} + \text{H}-\text{Bu}^t\text{+}$], 486.3 [$\text{M} + \text{Na}^+$]). Analysis by ^1H and ^{13}C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

δH (CDCl_3 at 298K); 1.24 (9 x $\text{C}(\text{CH}_3)_3$, s), 1.51-1.90 (2 H_γ + 2 H_δ , m), 3.38-3.48/3.49-3.58 (1 H_ϵ , dt), 3.62-3.74 (H_β , b), 3.95-4.02/4.06-4.14 (1 H_ϵ , dd), 4.24-4.78 (Fmoc H-9 + Fmoc CH_2 + 2 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, bm), 4.88/5.01 (H_α , dd, J 5.8), 5.25 (1 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, d, J 5.7), 5.37 (1 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, d, J 16.8), 5.88-6.00 (1 x $\text{COOCH}_2\text{CH}=\text{CH}_2$, m), 7.28-7.39 (2H aromatic, Fmoc H-2 and H-7), 7.39-7.46 (2H aromatic, Fmoc H-3 and H-6), 7.57-7.71 (2H aromatic, Fmoc H-1 and H-8), 7.78-7.86 (2H aromatic, Fmoc H-4 and H-5).

δC (CDCl_3 at 298K); 23.69/24.00 (d, C_δ), 28.38 (u, $\text{C}(\text{CH}_3)_3$), 28.65 (d, C_γ), 40.41/40.72 (d, C_ϵ), 47.61 (u, Fmoc C-9), 58.46 (u, C_α), 65.67 (d, $\text{COOCH}_2\text{CH}=\text{CH}_2$), 67.82 (u, C_β), 68.12 (d, Fmoc CH_2), 74.93 (q, $\text{C}(\text{CH}_3)_3$), 118.46/118.57 (d, $\text{COOCH}_2\text{CH}=\text{CH}_2$), 120.40 (u, Fmoc C-4 and C-5), 125.39 (u, Fmoc C-1 and C-8), 127.46 (u, Fmoc C-2 and C-7), 128.10 (u, Fmoc C-3

and C-6), 132.49 (u, $\text{COOCH}_2\text{CH}=\text{CH}_2$), 141.71 (q, Fmoc C-4' and C-5'), 144.12/144.35 (q, Fmoc C-1' and C-8'), 156.24 (q, OCON), 170.42/171.06 ($\text{COOCH}_2\text{CH}=\text{CH}_2$).

5 (2) Preparation of (2*R*, 3*S*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester.

(2*R*,3*S*) (3-*tert*-butoxy)pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester (1.42g, 3.07mmole) was dissolved in dry dichloromethane (25mL) with stirring. Tetrakis(triphenylphosphine) palladium (0) (71mg, 0.062mmole, 0.02eq) was added, followed by phenyltrihydrosilane (0.66g, 0.581mL, 6.14mmole, 2eq). After 1hr, dichloromethane (150mL) was added and the organics washed with 0.01N HCl (150mL), brine (150mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give a dark grey solid (2.0g). The crude solid was 10 purified over silica gel (75g) eluting with a gradient of heptane : ethyl acetate 2:1 → 1:2. Desired fractions were combined and reduced in vacuo to a white crystalline yield 1.07g (2.53mmole, 82.3%). TLC (single UV spot, $R_f = 0.25$, heptane : ethyl acetate 1:1), analytical HPLC $R_t = 21.306\text{mins}$, HPLC-MS (single main UV peak with $R_t = 10.269\text{mins}$, 368.2 [$\text{M} + \text{H}-\text{Bu}^{\text{t}}\text{+}$], 446.2 [$\text{M} + \text{Na}^{\text{+}}$], 869.3 [2M + Na] $^{\text{+}}$). Analysis by ^1H and ^{13}C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

δH (CDCl_3 at 298K); 1.32/1.41 (9 x $\text{C}(\text{CH}_3)_3$, ds), 1.43-1.59 (1 H_γ + 1 H_δ , m), 1.70-1.81 (1 H_δ , bm), 1.82-1.99 (1 H_γ , bm), 2.75-2.82/2.90-2.97 (1 H_ϵ , dt), 3.73-3.85 (H_β , b), 3.92-4.05 (1 H_ϵ , dd), 4.23-4.32 (Fmoc H-9), 4.40-4.58 (Fmoc CH_2 , bm), 4.60-4.62/5.02-5.04 (H $_\alpha$, dd, J5.7), 7.29-7.36 (2H aromatic, Fmoc H-2 and H-7), 7.39-7.44 (2H aromatic, Fmoc H-3 and H-6), 7.54-7.67 (2H aromatic, Fmoc H-1 and H-8), 7.77-7.82 (2H aromatic, Fmoc H-4 and H-5), 10.80-11.15 (COOH , bs).

δC (CDCl_3 at 298K); 23.71/24.24 (d, C_δ), 28.20/28.27 (u, $\text{C}(\text{CH}_3)_3$), 30.60/30.73 (d, C_γ), 40.50/40.79 (d, C_ϵ), 47.58/47.63 (u, Fmoc C-9), 58.20/58.44 (u, C_α), 67.77/68.33 (u, C_β), 68.67/68.87 (d, Fmoc CH_2), 78.48/78.67 (q, $\text{C}(\text{CH}_3)_3$), 120.30 (u, Fmoc C-4 and C-5),

125.16/125.27/125.52 (u, Fmoc C-1 and C-8), 127.42/127.48/127.59 (u, Fmoc C-2 and C-7), 128.04/128.10 (u, Fmoc C-3 and C-6), 141.57/141.69/141.78 (q, Fmoc C-4' and C-5'), 144.06/144.11/144.36/144.47 (q, Fmoc C-1' and C-8'), 155.73/156.49 (q, OCON), 169.26/169.55 (COOH).

5

(3) Preparation of (*2R, 3S*) (*3-tert-butoxy*)-2-(2-diazoacetyl)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester.

(*2R, 3S*) (*3-tert-butoxy*)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester (830mg, 1.96mmole) was dissolved with stirring in dry dichloromethane (20mL). The reaction was flushed with nitrogen and cooled to -15°C. Isobutylchloroformate (296mg, 2.16mmole in dry dichloromethane (2.5mL) and N-methylmorpholine (397mg, 3.92mmole in dry dichloromethane (2.5mL) were added simultaneously in 0.5mL aliquots over 15mins. Ethereal diazomethane (generated from diazald (2.5g, ~8mmole in diethyl ether (40mL)) onto sodium hydroxide (2.75g) in water (4.3mL) / ethanol (8.6mL) at 60°C). was added to the activated aminoacid solution and stirred at RT for 3hr, Acetic acid (~3mL) was added to quench the reaction, then *tert*-butylmethylether (100mL) was added, the organics washed with water (3 x 150mL), then dried (Na₂SO₄). The solvents were removed in vacuo to give a tacky pale yellow oil (910mg). The crude oil was purified over silica gel (75g) eluting with a gradient of heptane : ethyl acetate 4:1 → 3:1. Desired fractions were combined and reduced in vacuo to a pale yellow oil/solid, yield 560mg (1.25mmole, 63.9%). TLC (single main UV spot, R_f = 0.35, heptane : ethyl acetate 2:1), analytical HPLC R_t = 18.754min, HPLC-MS (UV peaks with R_t = 9.095mins, 364.2 [M + H]⁺, 386.1 [M + Na]⁺, 749.2 [2M + Na]⁺ and R_t = 10.856mins, 420.2 [M + H-N₂]⁺, 470.2 [M + Na]⁺, 917.3 [2M + Na]⁺).

10

15

20

25

30

Note that upon HPLC-MS analysis, m/z 364.2 corresponds to the desired bicyclic product (*3aR, 7aS*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9H-fluoren-9-ylmethyl ester.

Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

^1H (CDCl₃ at 298K); 1.29/1.46 (9 x C(CH₃)₃, ds), 1.40-1.85 (2H_y + 2H_δ, bm), 3.05/3.38 (1H_ε, dt), 3.39-3.44/3.62-3.69 (H_β, dm), 3.90-3.97 (1H_ε, dd), 4.05-4.07/4.78-4.83 (H_α, bm), 4.24-4.33 (Fmoc H-9), 4.36-4.42/4.46-4.51 (1 x Fmoc CH₂, dm), 4.61-4.68 (1 x Fmoc CH₂, m), 4.89/5.90 (COCH=N₂, s + bs), 7.28-7.39 (2H aromatic, Fmoc H-2 and H-7), 7.40-7.44 (2H aromatic, Fmoc H-3 and H-6), 7.53-7.67 (2H aromatic, Fmoc H-1 and H-8), 7.76-7.81 (2H aromatic, Fmoc H-4 and H-5).
 ^{13}C (CDCl₃ at 298K); 23.94/24.51 (d, C_δ), 28.38/28.53 (u, C(CH₃)₃), 29.23/29.84 (d, C_γ), 40.83/41.45 (d, C_ε), 47.57/47.64 (u, Fmoc C-9), 55.50/56.38 (u, COCH=N₂), 61.69/62.66 (u, C_α), 66.85/68.20 (d, Fmoc CH₂), 69.35/69.61 (u, C_β), 75.11/75.54 (q, C(CH₃)₃), 120.29/120.32 (u, Fmoc C-4 and C-5), 124.85/125.25/125.53 (u, Fmoc C-1 and C-8), 127.46/127.59 (u, Fmoc C-2 and C-7), 127.97/128.03/128.07 (u, Fmoc C-3 and C-6), 141.62/141.69/141.73 (q, Fmoc C-4' and C-5'), 144.24/144.31/144.50/144.61 (q, Fmoc C-1' and C-8'), 155.68/156.89 (q, OCON), 191.90/192.37 (COCH=N₂).

(4) Cyclisation to (3a*R*, 7a*S*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester.

A solution of lithium chloride (494mg, 11.6mmole) in water (3mL) and acetic acid (12mL) was added to (2*R*, 3*S*) (3-*tert*-butoxy)-2-(2-diazoacetyl) pyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester (520mg, 1.16mmole). Gas was evolved and the yellow oily solid dissolved over 1hr to give a virtually colourless solution. After 90mins, chloroform (150mL) was added and the organics washed with NaHCO₃ (2 x 150mL), brine (150mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a white crystalline solid (390mg). The crude solid was purified over silica gel (75g) eluting with a gradient of heptane : ethyl acetate 3:1 → 2:1. Desired fractions were combined and reduced in vacuo to a white crystalline solid, yield 340mg (0.94mmole, 47.7% from starting acid). TLC (single UV spot, R_f = 0.25, heptane : ethyl acetate 2:1), analytical HPLC Rt = 18.563mins, HPLC-MS

(single UV peak with R_t = 9.074mins, 364.2 $[M + H]^+$, 386.2 $[M + Na]^+$). Analysis by 1H and ^{13}C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

5 1H ($CDCl_3$ at 298K); 1.20-1.38 (1H $_\gamma$ + 1H $_\delta$, m), 1.51-1.68 (1H $_\delta$, bm), 1.96-2.08 (1H $_\gamma$, bm), 2.40-2.52/2.53-2.67 (1H $_\epsilon$, m), 3.87 ($COCH_2A$, d, J 16.5), 3.85-3.95 (1H $_\epsilon$, b), 4.09 (Fmoc H-9, bt), 4.14 (H $_\beta$, b), 4.21-4.46 (Fmoc CH $_2$ + $COCH_2B$, bm), 4.62-4.70/5.00-5.09 (H $_\alpha$, 2 x b), 7.23-7.27 (2H aromatic, Fmoc H-2 and H-7), 7.32-7.35 (2H aromatic, Fmoc H-3 and H-6), 7.41-7.53 (2H aromatic, Fmoc H-1 and H-8), 7.69-7.71 (2H aromatic, Fmoc H-4 and H-5).

10 ^{13}C ($CDCl_3$ at 298K); 22.08 (d, C $_\delta$), 26.61 (d, C $_\gamma$), 41.67 (d, C $_\epsilon$), 47.58 (u, Fmoc C-9), 60.54 (u, C $_\alpha$), 67.55 (d, Fmoc CH $_2$), 68.40 (d, COCH $_2O$), 72.61 (u, C $_\beta$), 120.39 (u, Fmoc C-4 and C-5), 125.42 (u, Fmoc C-1 and C-8), 127.51 (u, Fmoc C-2 and C-7), 128.14 (u, Fmoc C-3 and C-6), 141.73 (q, Fmoc C-4' and C-5'), 144.16 (q, Fmoc C-1' and C-8'), 156.20 (q, OCON), 211.64 (q, COCH $_2O$).

Following the general details from **Scheme 2**, the required bicyclic building block (3aR, 7aS) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-yl 20 methyl ester was converted to building block-linker construct as follows:

25 (3aR, 7aS) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (290mg, 0.80mmole) was dissolved in a mixture of ethanol (14.0mL) and water (2.0mL) containing sodium acetate trihydrate (163mg, 1.198mmole, 1.5eq). 4-[[*(hydrazinocarbonyl)amino*]methyl]cyclohexanecarboxylic acid trifluoroacetate (263mg, 0.80mmole, 1.0eq, Murphy, A. M. *et al*, *J. Am. Chem. Soc.*, 114, 3156-3157, 1992) was added and the mixture refluxed for 4hrs. Chloroform (150mL) was added and the organics washed with HCl (150mL, ~ pH3), dried (Na_2SO_4) and reduced in vacuo to provide crude building block-linker construct as 30 an off-white crystalline solid. Yield 450mg, analytical HPLC 2 peaks R_t = 17.109 (67.6%) and 18.565mins (26.3%) (cis / trans geometrical isomers), HPLC-MS (2 x

UV peak with Rt = 8.069 and 9.050mins, 561.2 [M + H]⁺). Crude construct was used directly for construct loading.

Following the general details from Scheme 2, the required building block-linker
5 construct was attached to the solid phase providing loaded building block-linker
construct as follows:

Building block-linker construct (0.680mmoles), 2-(1H-benzotriazole-1-yl)-1,1,3,3-
10 tetramethyluroniumhexafluoro phosphate (HBTU, 258mg, 0.680mmole), 1-
hydroxybenzotriazole hydrate and (HOBT, 105mg, 0.680mmole) were dissolved in
dimethylformamide (3mL) and N-methylmorpholine (NMM, 150μL, 1.36mmole)
added. After pre-activation for 5 minutes, free amine gears (190 x 1.2μmole) were
added, followed by dimethylformamide (17.5mL) and left overnight. The spent
coupling solution was then added to free amine crowns (18 x 10μmole) and left
15 overnight. Standard washing and analyses indicated quantitative loading in both
cases.

Following the general details from Scheme 2, the required loaded building block-
linker construct was elaborated on the solid phase as follows:

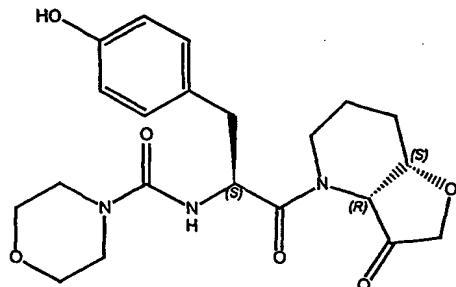
20

Loaded construct was elaborated to EXAMPLE 91 (3aR, 7aS) Morpholine-4-
carboxylic acid [1R-benzylsulfanyl methyl-2-oxo-2-(3-oxohexahydrofuro[3,2-b]
pyridin-4-yl)ethyl]amide by standard Fmoc deprotection and sequential coupling
with Fmoc-Cys(SBzl)-OH then morpholine-4-carbonylchloride. The crude example
25 was cleaved and analysed (see general techniques). HPLC Rt = 15.59mins (>80%),
HPLC-MS 449.2 [M + H]⁺.

The following examples (132 – 156) were prepared as detailed for EXAMPLE 131,
coupling with the required reagents to provide the full length molecule.

30

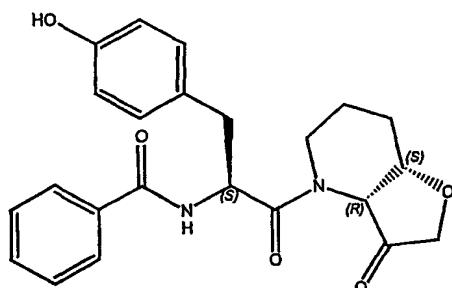
EXAMPLE 132. (3a*R*, 7a*S*) Morpholine-4-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



HPLC-MS 418.2 [M + H]⁺.

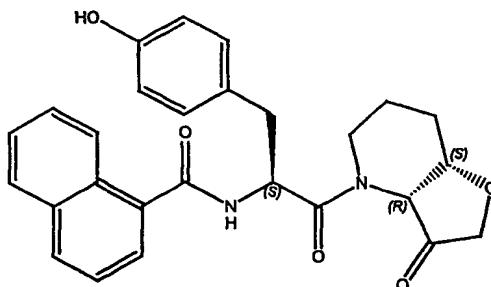
5

EXAMPLE 133. (3a*R*, 7a*S*) *N*-[1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide



10 HPLC Rt = 12.67mins (>80%), HPLC-MS 409.1 [M + H]⁺.

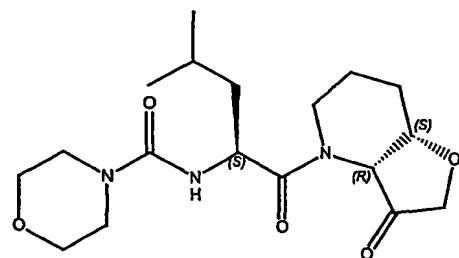
EXAMPLE 134. (3a*R*, 7a*S*) Naphthalene-1-carboxylic acid [1*S*-(4-hydroxybenzyl)-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



-210-

HPLC Rt = 14.87mins (>80%), HPLC-MS 459.2 [M + H]⁺.

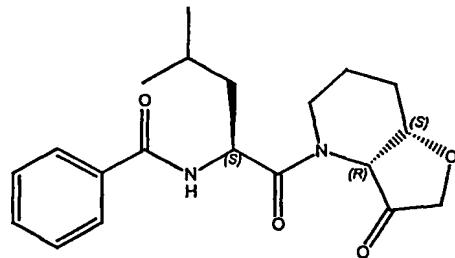
EXAMPLE 135. (3a*R*, 7a*S*) Morpholine-4-carboxylic acid [3-methyl-1*S*-(3-oxo-hexa hydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



5

HPLC-MS 368.2 [M + H]⁺, 390.2 [M + Na]⁺.

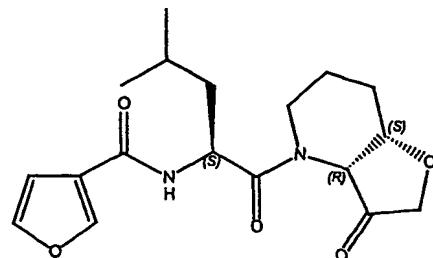
EXAMPLE 136. (3a*R*, 7a*S*) *N*-[3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide



10

HPLC Rt = 15.40mins (>80%), HPLC-MS 359.2 [M + H]⁺.

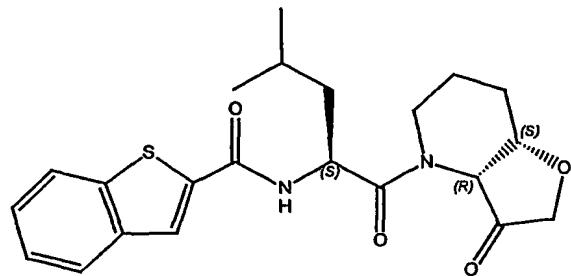
EXAMPLE 137. (3a*R*, 7a*S*) Furan-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



15

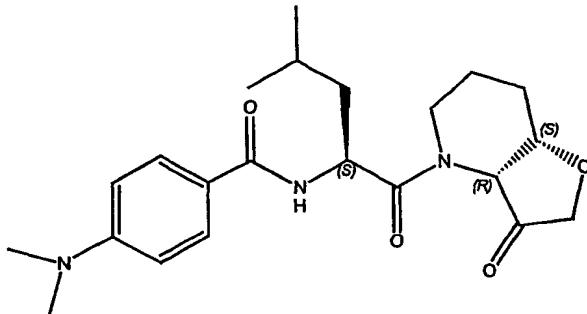
HPLC Rt = 13.74mins (>85%), HPLC-MS 349.2 $[M + H]^+$, 371.2 $[2M + Na]^+$.

EXAMPLE 138. (3a*R*, 7a*S*) Benzo[*b*]thiophene-2-carboxylic acid [3-methyl-1*S*-(3-
5 oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



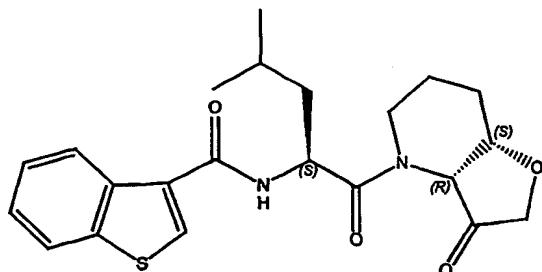
HPLC Rt = 18.52mins (>80%), HPLC-MS 415.2 $[M + H]^+$, 851.3 $[2M + Na]^+$.

10 EXAMPLE 139. (3a*R*, 7a*S*) 4-Dimethylamino-N-[3-methyl-1*S*-(3-oxo-hexahydro
furo[3,2-*b*]pyridine-4-carbonyl) butyl]benzamide



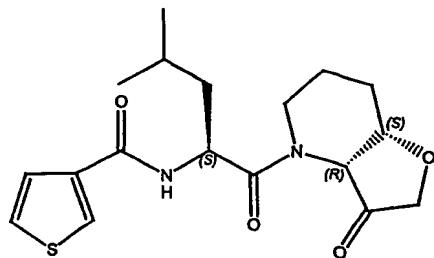
HPLC Rt = 13.55mins (>80%), HPLC-MS 402.2 $[M + H]^+$, 825.3 $[2M + Na]^+$.

15 EXAMPLE 140. (3a*R*, 7a*S*) Benzo[*b*]thiophene-3-carboxylic acid [3-methyl-1*S*-(3-
oxo-hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



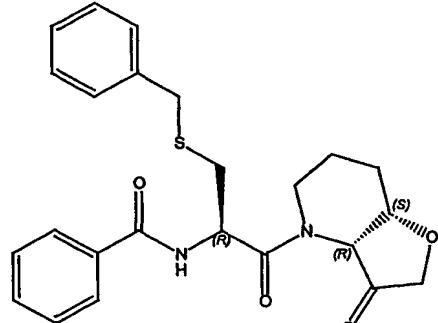
HPLC Rt = 18.26mins (>80%), HPLC-MS 415.2 [M + H]⁺, 851.3 [2M + Na]⁺.

EXAMPLE 141. (3a*R*, 7a*S*) Thiophene-3-carboxylic acid [3-methyl-1*S*-(3-oxo-hexa
5 hydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



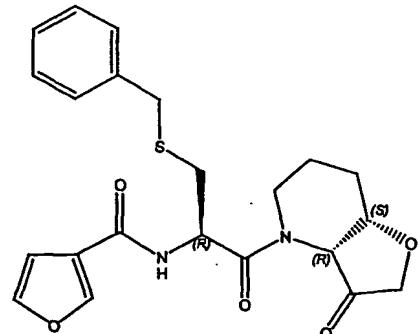
HPLC Rt = 14.80mins (>80%), HPLC-MS 365.2 [M + H]⁺, 387.2 [M + Na]⁺.

EXAMPLE 142. (3a*R*, 7a*S*) *N*-[1*R*-benzylsulfanyl methyl-2-oxo-2-(3-oxo-hexahydro
10 furo[3,2-*b*]pyridin-4-yl)ethyl]benzamide



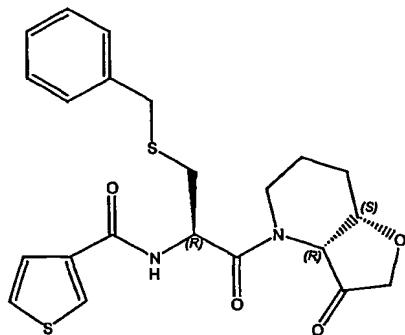
HPLC Rt = 17.78mins (>80%), HPLC-MS 439.2 [M + H]⁺, 899.3 [2M + Na]⁺.

EXAMPLE 143. (3a*R*, 7a*S*) Furan-3-carboxylic acid-[1*R*-benzylsulfanyl methyl-2-
oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



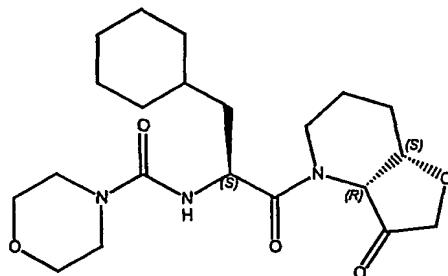
HPLC Rt = 16.41mins (>85%), HPLC-MS 429.6 [M + H]⁺, 451.5 [M + Na]⁺.

EXAMPLE 144. (3a*R*, 7a*S*) Thiophene-3-carboxylic acid-[1*R*-benzylsulfanyl methyl-
5 2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



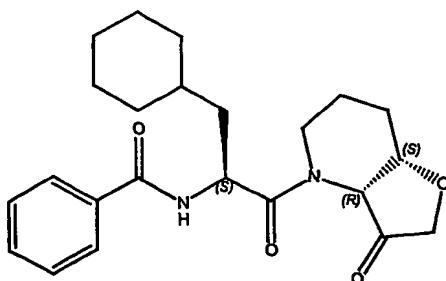
HPLC Rt = 17.23mins (>80%), HPLC-MS 445.1 [M + H]⁺, 911.2 [2M + Na]⁺.

EXAMPLE 145. (3a*R*, 7a*S*) Morpholine-4-carboxylic acid [1*S*-cyclohexylmethyl-2-
10 2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



HPLC-MS 408.2 [M + H]⁺.

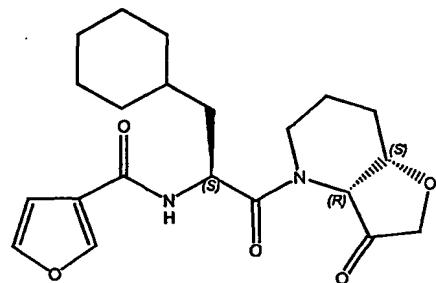
EXAMPLE 146. (3a*R*, 7a*S*) *N*-[1*S*-cyclohexylmethyl-2-oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]benzamide



HPLC Rt = 18.47mins (>80%), HPLC-MS 399.2 [M + H]⁺, 819.3 [2M + Na]⁺.

EXAMPLE 147. (3a*R*, 7a*S*) Furan-3-carboxylic acid [1*S*-cyclohexylmethyl-2-oxo-2-

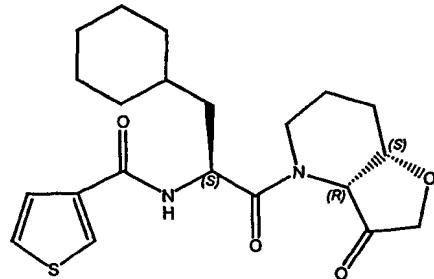
5 (3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



HPLC Rt = 17.12mins (>80%), HPLC-MS 389.2 [M + H]⁺.

EXAMPLE 148. (3a*R*, 7a*S*) Thiophene-3-carboxylic acid [1*S*-cyclohexylmethyl-2-

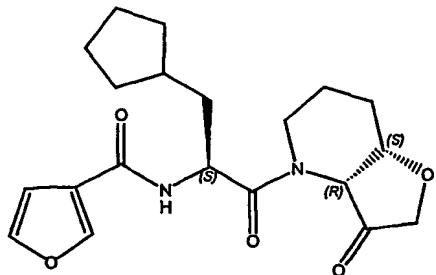
10 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



HPLC Rt = 18.05mins (>85%), HPLC-MS 405.2 [M + H]⁺, 831.2 [2M + Na]⁺.

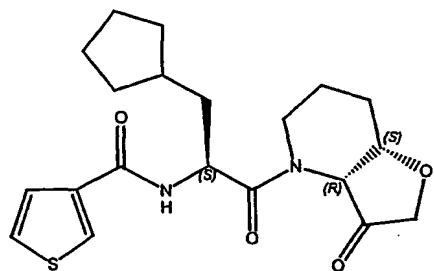
EXAMPLE 149. (3a*R*, 7a*S*) Furan-3-carboxylic acid [1*S*-cyclopentylmethyl-2-oxo-2-

15 (3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



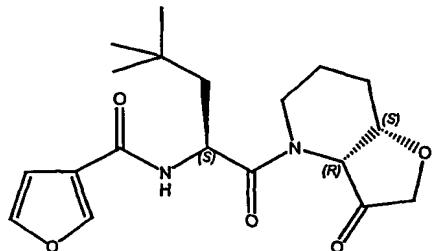
HPLC Rt = 15.84mins (>85%), HPLC-MS 375.2 $[M + H]^+$, 771.3 $[2M + Na]^+$.

EXAMPLE 150. (3a*R*, 7a*S*) Thiophene-3-carboxylic acid [1*S*-cyclopentylmethyl-2-
5 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl]amide



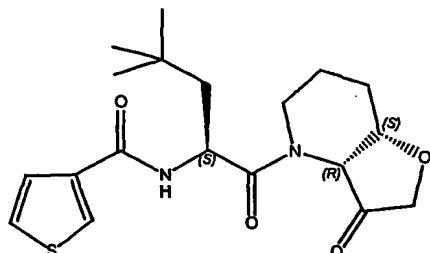
HPLC Rt = 16.78mins (>85%), HPLC-MS 391.1 $[M + H]^+$, 803.3 $[2M + Na]^+$.

EXAMPLE 151. (3a*R*, 7a*S*) Furan-3-carboxylic acid [3,3-dimethyl-1*S*-(3-oxo-hexa-
10 hydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



HPLC Rt = 15.05mins (>85%), HPLC-MS 363.2 $[M + H]^+$, 747.4 $[2M + Na]^+$.

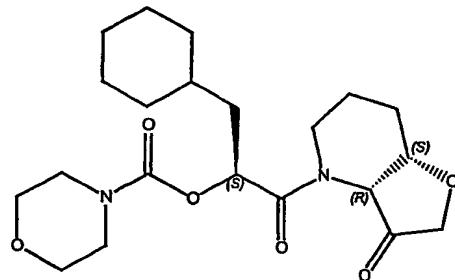
EXAMPLE 152. (3a*R*, 7a*S*) Thiophene-3-carboxylic acid [3,3-dimethyl-1*S*-(3-oxo-
15 hexahydrofuro[3,2-*b*]pyridine-4-carbonyl) butyl]amide



HPLC Rt = 15.76mins (>80%), HPLC-MS 379.2 [M + H]⁺, 779.3 [2M + Na]⁺.

EXAMPLE 153. (3a*R*, 7a*S*) Morpholine-4-carboxylic acid 1*S*-cyclohexylmethyl-2-

5 oxo-2-(3-oxo-hexahydrofuro[3,2-*b*]pyridin-4-yl)ethyl ester

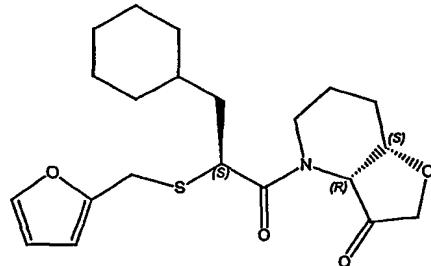


HPLC-MS 409.2 [M + H]⁺, 839.5 [2M + Na]⁺.

As detailed for EXAMPLE 127, compound (33) was coupled under standard
10 conditions (following Fmoc removal) to the (3a*R*, 7a*S*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded
building block-linker construct (22), then cleaved to provide EXAMPLE 153.

EXAMPLE 154 (2*S*, 3*aR*, 7*aS*) 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulfanyl)

15 propionyl]hexahydrofuro[3,2-*b*]pyridin-3-one



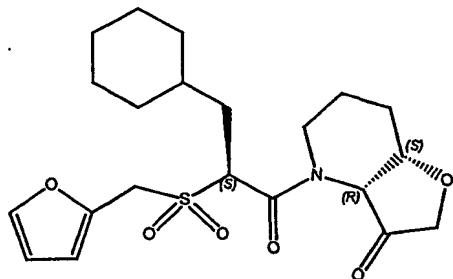
HPLC-MS 392.1 [M + H]⁺, 805.3 [2M + Na]⁺.

As detailed for EXAMPLE 128, compound (41) was coupled under standard

20 conditions (following Fmoc removal) to the (3a*R*, 7a*S*) 3-oxo-hexahydrofuro[3,2-

b]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded building block-linker construct (22), then cleaved to provide EXAMPLE 154.

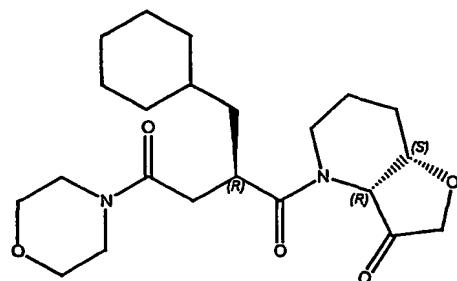
EXAMPLE 155. (2*S*, 3*aR*, 7*aS*) 4-[3-Cyclohexyl-2-(furan-2-ylmethanesulphonyl)
5 propionyl]hexahydrofuro[3,2-*b*]pyridin-3-one



HPLC Rt = 18.8 – 19.4mins (>90%), HPLC-MS 424.1 [M + H]⁺, 869.2 [2M + Na]⁺.

As detailed for EXAMPLE 129, compound (41) was coupled under standard
10 conditions (following Fmoc removal) to the (3*aR*, 7*aS*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded building block-linker construct (22). The intermediate loaded thioether (1.2μmole gear) was oxidised with m-chloroperbenzoic acid (5eq, 65% reagent, 1.6mg) in dichloromethane (200μL) for 5hrs, followed by standard washing and then cleaved to
15 provide EXAMPLE 155.

EXAMPLE 156. (3*aR*, 7*aS*) 2*R*-Cyclohexylmethyl-4-morpholin-4-yl-1-(3-oxo-hexa-
hydrofuro[3,2-*b*] pyridin-4-yl)butane-1,4-dione



20 HPLC-MS 407.2 [M + H]⁺, 833.3 [2M + Na]⁺.

As detailed for EXAMPLE 130, compound (36) was coupled under standard conditions (following Fmoc removal) to the (3a*R*, 7a*S*) 3-oxo-hexahydrofuro[3,2-*b*]pyridine-4-carboxylic acid 9*H*-fluoren-9-ylmethyl ester equivalent of loaded 5 building block-linker construct (22), then cleaved to provide EXAMPLE 156.

EXAMPLE A. Assays for Cysteine Protease Activity

The compounds of this invention may be tested in one of a number of literature based 10 biochemical assays that are designed to elucidate the characteristics of compound inhibition. The data from these types of assays enables compound potency and the rates of reaction to be measured and quantified. This information, either alone or in combination with other information, would allow the amount of compound required to produce a given pharmacological effect to be determined.

15

General materials and methods

Unless otherwise stated, all general chemicals and biochemicals were purchased from either the Sigma Chemical Company, Poole, Dorset, U.K. or from Fisher 20 Scientific UK, Loughborough, Leicestershire, U.K. Absorbance assays were carried out in flat-bottomed 96-well plates (Spectra; Greiner Bio-One Ltd., Stonehouse, Gloucestershire, U.K.) using a SpectraMax PLUS384 plate reader (Molecular Devices, Crawley, U.K.). Fluorescence high throughput assays were carried out in either 384-well microtitre plates (Corning Costar 3705 plates, Fisher Scientific) or 25 96-well 'U' bottomed Microfluor W1 microtitre plates (Thermo Labsystems, Ashford, Middlesex, U.K.). Fluorescence assays were monitored using a SpectraMax Gemini fluorescence plate reader (Molecular Devices). For substrates employing either a 7-amino-4-methylcoumarin (AMC) or a 7-amino-4-trifluoromethylcoumarin (AFC) fluorophore, assays were monitored at an excitation wavelength of 365 nm and an emission wavelength of 450 nm and the fluorescence 30 plate reader calibrated with AMC. For substrates employing a 3-amino-benzoyl (Abz) fluorophore, assays were monitored at an excitation wavelength of 310 nm and an emission wavelength of 445 nm; the fluorescence plate reader calibrated with 3-amino-benzamide (Fluka). Unless otherwise indicated, all the peptidase substrates

were purchased from Bachem UK, St. Helens, Merseyside, UK. Substrates utilizing fluorescence resonance energy transfer methodology (*i.e.* FRET-based substrates) were synthesized at Incenta Limited using published methods (Atherton & Sheppard, *Solid Phase Peptide Synthesis*, IRL Press, Oxford, U.K., 1989) and employed Abz 5 (2-aminobenzoyl) as the fluorescence donor and 3-nitro-tyrosine [Tyr(NO₂)] as the fluorescence quencher (Meldal, M. and Breddam, K., *Anal. Biochem.*, **195**, 141-147, 1991). Hydroxyethylpiperazine ethanesulfonate (HEPES), tris-hydroxymethyl aminomethane (tris) base, bis-tris-propane and all the biological detergents (*e.g.* CHAPS, zwittergents, *etc.*) were purchased from CN Biosciences UK, Beeston, 10 Nottinghamshire, U.K. Glycerol was purchased from Amersham Pharmacia Biotech, Little Chalfont, Buckinghamshire, U.K. Stock solutions of substrate or inhibitor were made up to 10 mM in 100 % dimethylsulfoxide (DMSO) (Rathburns, Glasgow, U.K.) and diluted as appropriately required. In all cases the DMSO concentration in 15 the assays was maintained at less than 1% (vol./vol.).

Assay protocols were based on literature precedent (Table 1; Barrett, A.J., Rawlings, N.D. and Woessner, J.F., 1998, *Handbook of Proteolytic Enzymes*, Academic Press, London and references therein) and modified as required to suit local assay 20 protocols. Enzyme was added as required to initiate the reaction and the activity, as judged by the change in fluorescence upon conversion of substrate to product, was monitored over time. All assays were carried out at 25±1°C.

Table 1. *The enzyme assays described herein were carried out according to literature precedents.*

Enzyme	Buffer	Substrate	Reference
Cathepsin B	I	Z-Phe-Arg-AMC	a, b
Cathepsin H	II	Bz-Phe-Val-Arg-AMC	a, b
Cathepsin L	I	Ac-Phe-Arg-AMC	b, c
Cathepsin S	I	Boc-Val-Leu-Lys-AMC	c, d
Caspase 1	III	Ac-Leu-Glu-His-Asp-AMC	e
Caspase 2	III	Z-Val-Asp-Val-Ala-Asp-AFC	f
Caspase 3	III	Ac-Asp-Glu-Val-Asp-AMC	g, h

Caspase 4	III	Suc-Tyr-Val-Ala-Asp-AMC	f
Caspase 5	III	Ac-Leu-Glu-His-Asp-AMC	
Caspase 6	III	Ac-Val-Glu-Ile-Asp-AMC	i, j, k
Caspase 7	III	Ac-Asp-Glu-Val-Asp-AMC	
Caspase 8	III	Ac-Ile-Glu-Thr-Asp-AMC	l
Caspase 9	III	Ac-Leu-Glu-His-Asp-AMC	
Caspase 10	III	Ac-Ile-Glu-Thr-Asp-AMC	
Cruzipain	IV	D-Val-Leu-Lys-AMC	m, n
CPB2.8 Δ CTE	XI	Pro-Phe-Arg-AMC	q
<i>S. Aureus</i> Extracellular cysteine peptidase	I	Abz-Ile-Ala-Ala-Pro- Tyr(NO ₂)-Glu-NH ₂	o
Clostripain		Z-Gly-Gly-Arg-AMC	p
FMDV LP	V	Abz-Arg-Lys-Leu-Lys-Gly- Ala-Gly-Ser-Tyr(NO ₂)-Glu- NH ₂	r
Trypsin	VI	Z-Gly-Gly-Arg-AMC	s
Calpain μ	VII	Abz-Ala-Asn-Leu-Gly-Arg-Pro- Ala-Leu-Tyr(NO ₂)-Asp-NH ₂	t
Calpain m	VIII	Abz-Lys-Leu-Cys(Bzl)-Phe-Ser- Lys-Gln-Tyr(NO ₂)-Asp-NH ₂	t
Cathepsin K	IX	Z-Phe-Arg-AMC	u
Cathepsin X	X		v, w

I: 10 mM BTP, pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1 mM CaCl₂

II: 10 mM BTP, pH 6.5 containing 1 mM EDTA, 142 mM NaCl, 1 mM DTT, 1 mM 5 CaCl₂, 0.035 mM Zwittergent 3-16

III: 50mM HEPES pH 7.2, 10% Glycerol, 0.1% CHAPS, 142 mM NaCl, 1 mM EDTA, 5 mM DTT

IV: 100 mM sodium phosphate, pH 6.75 containing 1 mM EDTA and 10 mM L-cysteine

V: 50 mM trisacetate, pH 8.4 containing 1 mM EDTA, 10 mM L-cysteine and 0.25% (w/v) CHAPS

VI: 10 mM HEPES, pH 8.0 containing 5 mM CaCl₂

VII: 10 mM HEPES, pH 7.5 containing 2 mM 2-mercaptoethanol and 100 µM CaCl₂

5 VIII: 10 mM HEPES, pH 7.5 containing 2 mM 2-mercaptoethanol and 200 µM CaCl₂

IX: 100 mM sodium acetate; pH 5.5 containing 10 mM L-cysteine and 1 mM EDTA

X: 100 mM sodium acetate; pH 5.5 containing 10 mM L-cysteine; 0.05% (w/v) Brij 35 and 1 mM EDTA

10 XI: 100 mM sodium acetate; pH 5.5 containing 10 mM L-cysteine; 142 mM sodium chloride and 1 mM EDTA

^a Barrett, A.J., *Biochem. J.*, 187, 909-912, 1980

^b Barrett, A.J. and Kirschke, H., *Methods Enzymol.*, 80, 535-561, 1981

15 ^c Quibell, M. and Taylor, S., *WO0069855*, 2000

^d Bromme, D., Steinert, ., Freibe, S., Fittkau, S., Wiederanders, B., and Kirschke, H., *Biochem. J.*, 264, 475-481, 1989

^e Rano, T.A., *et. al.*, *Chem. Biol.*, 4, 149, 1997

^f Talanian, R.V., *et. al.*, *J. Biol. Chem.*, 272, 9677, 1997

20 ^g Lazebnik, Y.A., Kaufmann, S.H., Desnoyers, S., Poirer, G.G. and Earnshaw, W.C., *Nature*, 371, 768-774, 1994

^h Han, Z., *et. al.*, *J. Biol. Chem.*, 272, 13432, 1997

ⁱ Takahashi, A., *et. al.*, *PNAS*, 93, 8395, 1996

^j Martins, L.M., *et. al.*, *J. Biol. Chem.*, 272, 7421, 1997

25 ^k Nagata, S., *Cell*, 88, 355, 1997

^l Harris, J.L., *et. al.*, *J. Biol. Chem.*, 273, 27364, 1998

^m Cazzulo, J.J., Cazzulo Franke, M.C., Martinez, J. and Franke de Cazzulo, B.M., *Biochim. Biophys. Acta*, 1037, 186-191, 1990

30 ⁿ Cazzulo, J.J., Bravo, M., Raimondi, A., Engstrom, U., Lindeberg, G. and Hellman, U., *Cell Mol. Biol.*, 42, 691-696, 1996

^o Potempa, J., Dubin, A., Korzus, G. and Travis, J., *Biochem. J.*, 263, 2664-2667, 1988

^p Kembhavi, A.A., Buttle, D.J., Rauber, P. and Barrett, A.J., *FEBS Lett.*, 283, 277-280, 1991

^q Alves, L.C., *et. al.*, *Mol. Biochem. Parasitol.*, 116, 1-9, 2001.

^r Guarné, *et.al.*, *J. Mol. Biol.*, 302, 1227-1240, 2000.

5 ^s Halfon and Craik, (Barret, Rawlings and Woessner, eds.), in *Handbook of Proteolytic Enzymes*, Academic Press, London, 12-21, 1998.

^t Sasaki, *et. al.*, (1984), *J. Biol. Chem.*, 259, 12489-12494, 1984.

^u Bossard, M.J., *et. al.*, *J. Biol. Chem.*, 21, 12517-12524, 1996

^v Santamaria, I., *et. al.*, *J. Biol. Chem.*, 273, 16816-16823, 1998

10 ^w Klemencic, J., *et al.*, *Eur.J.Biochem.*, 267, 5404-5412, 2000

Trypanosoma cruzi cruzipain peptidase activity assays

Wild-type cruzipain, derived from *Trypanosoma cruzi* Dm28 epimastigotes, was obtained from Dr. Julio Scharfstein (Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil). Activity assays were carried out in 100 mM sodium phosphate, pH 6.75 containing 1 mM EDTA and 10 mM L-cysteine using 2.5 nM enzyme. Ac-Phe-Arg-AMC ($K_M^{app} \approx 12 \mu M$) and D-Val-Leu-Lys-AMC ($K_M^{app} \approx 4 \mu M$) were used as the substrates. Routinely, Ac-FR-AMC was used at a concentration equivalent to K_M^{app} and D-Val-Leu-Lys-AMC was used at a concentration of 25 μM . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

25 *Leishmania mexicana* cysteine protease B (CPB) peptidase activity assays

Wild-type recombinant CPB without the C-terminal extention (*i.e.* CPB2.8 Δ CTE; Sanderson, S.J., *et. al.*, *Biochem. J.*, 347, 383-388, 2000) was obtained from Dr. Jeremy Mottram (Wellcome Centre for Molecular Parasitology, The Anderson College, University of Glasgow, Glasgow, U.K.). Activity assays were carried out in 100 mM sodium acetate; pH 5.5 containing 1 mM EDTA; 200 mM NaCl and 10 mM DTT (Alves, L.C., *et. al.*, *Mol. Biochem. Parasitol.*, 116, 1-9, 2001) using 0.25 nM enzyme. Pro-Phe-Arg-AMC ($K_M^{app} \approx 38 \mu M$) was used as the substrate at a

concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

5 Cathepsin peptidase activity assays

Bovine cathepsin S, human cathepsin L, human cathepsin H and human cathepsin B were obtained from CN Biosciences. Recombinant human cathepsin S, human cathepsin K and human cathepsin X were obtained from Dr. Boris Turk (Josef Stefan 10 Institute, Ljubljana, Slovenia). Unless otherwise stated, all peptidase activity assays were carried out in 10 mM bis-tris-propane (BTP), pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1 mM CaCl₂. Human cathepsin H activity assays were carried out in 10 mM BTP pH 6.5, 142 mM NaCl₂, 1 mM CaCl₂, 1 mM EDTA, 1 mM DTT, 0.035 mM Zwittergent 3-16. Human cathepsin K assays were carried out 15 in 100 mM sodium acetate; pH 5.5 containing 20 mM L-cysteine and 1 mM EDTA (Bossard, M.J., *et. al.*, *J. Biol. Chem.*, 21, 12517-12524, 1996). Human cathepsin X assays were carried out in 100 mM sodium acetate; pH 5.5 containing 20 mM L-cysteine; 0.05% (w/v) Brij 35 and 1 mM EDTA (Santamaria, I., *et. al.*, *J. Biol. Chem.*, 273, 16816-16823, 1998; Klemencic, J, *et al.*, *Eur. J. Biochem.*, 267, 5404-20 5412, 2000). The final enzyme concentrations used in the assays were 0.5 nM bovine cathepsin S, 1 nM cathepsin L, 0.1 nM cathepsin B, 0.25nM Cathepsin K; 1 nM cathepsin X and 10 nM cathepsin H. For the inhibition assays, the substrates used for cathepsin S, cathepsin L, cathepsin B, cathepsin K and cathepsin H were boc-Val-Leu-Lys-AMC ($K_M^{app} \approx 30 \mu\text{M}$), Ac-Phe-Arg-AMC ($K_M^{app} \approx 20 \mu\text{M}$), Z-25 Phe-Arg-AMC ($K_M^{app} \approx 40 \mu\text{M}$), Z-Leu-Arg-AMC ($K_M^{app} \approx 2\mu\text{M}$); Bz-Phe-Val-Arg-AMC ($K_M^{app} \approx 150 \mu\text{M}$) respectively. In each case the substrate concentration used in each assay was equivalent to the K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

30

Trypsin peptidase activity assays

Human pancreatic trypsin (iodination grade; CN Biosciences) activity assays were carried out in 10 mM HEPES, pH 8.0 containing 5 mM CaCl₂ using 0.1 nM trypsin. For the inhibition assays, Z-Gly-Gly-Arg-AMC ($K_M^{app} \approx 84 \mu\text{M}$) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Clostripain peptidase activity assays

10 Clostripain (Sigma) activity assays were carried out in 10 mM BTP, pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1mM CaCl₂ using 0.3 nM enzyme. For the inhibition assays, Z-Gly-Gly-Arg-AMC ($K_M^{app} \approx 100 \mu\text{M}$) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Calpain peptidase activity assays

20 Calpain (human erythrocyte μ -calpain and porcine kidney m-calpain; CN Biosciences) activity assays were carried out in 10 mM HEPES, pH 7.5 containing 2 mM 2-mercaptoethanol and CaCl₂ using 25 nM of either enzyme (Sasaki, *et. al.*, *J. Biol. Chem.*, **259**, 12489-12494, 1984). For μ -calpain inhibition assays, the buffer contained 100 μM CaCl₂ and Abz-Ala-Asn-Leu-Gly-Arg-Pro-Ala-Leu-Tyr(NO₂)-Asp-NH₂ ($K_M^{app} \approx 20 \mu\text{M}$; Incenta Limited) was used as the substrate. For m-calpain inhibition assays, the assay buffer contained 200 μM CaCl₂ and Abz-Lys-Leu-Cys(Bzl)-Phe-Ser-Lys-Gln-Tyr(NO₂)-Asp-NH₂ ($K_M^{app} \approx 22 \mu\text{M}$; Incenta Limited) was used as the substrate. In both cases the substrate concentration employed in the assays was equivalent to the K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Extracellular *S. aureus* V8 cysteine peptidase (staphylopain) peptidase activity assays

S. aureus V8 was obtained from Prof. S. Arvidson, Karolinska Institute, Stockholm, 5 Sweden. Extracellular *S. aureus* V8 cysteine peptidase (staphylopain) activity assays were carried out using partially purified *S. aureus* V8 culture supernatant (obtained from Dr. Peter Lambert, Aston University, Birmingham, U.K.). Activity assays were carried out in 10 mM BTP, pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1mM CaCl₂ using two-times diluted partially purified extract. 10 For the inhibition assays, Abz-Ile-Ala-Ala-Pro-Tyr(NO₂)-Glu-NH₂ ($K_M^{app} \approx 117 \mu\text{M}$; Incenta Limited) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

15 Foot-and-mouth disease leader peptidase (FMDV-LP) activity assays

Recombinant wild-type FMDV-LP was obtained from Dr. Tim Skern (Institut für Medizinische Biochemie, Abteilung für Biochemie, Universtät Wien, Wien, Austria). Activity assays were carried out in 50 mM trisacetate, pH 8.4 containing 1 mM 20 EDTA, 10 mM L-cysteine and 0.25% (w/v) CHAPS using 10 nM enzyme. For the inhibition assays, Abz-Arg-Lys-Leu-Lys-Gly-Ala-Gly-Ser-Tyr(NO₂)-Glu-NH₂ ($K_M^{app} \approx 51 \mu\text{M}$, Incenta Limited) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

25

Caspase peptidase activity assays

Caspases 1-10 were obtained from CN Biosciences or BioVision Inc. (Mountain View, CA, USA) and all assays were carried out in 50mM HEPES; pH 7.2, 10% 30 (v/v) glycerol, 0.1% (w/v) CHAPS, 142 mM NaCl, 1 mM EDTA, 5 mM dithiothreitol (DTT) using 0.1-1 U per assay. For caspase 1, Ac-Leu-Glu-His-Asp-AMC was used as the substrate; for caspase 2, Z-Val-Asp-Val-Ala-Asp-AFC was used as the substrate; for caspase 3, Ac-Asp-Glu-Val-Asp-AMC was used as the

substrate; for caspase 4, Suc-Tyr-Val-Ala-Asp-AMC was used as the substrate; for caspase 5, Ac-Leu-Glu-His-Asp-AMC was used as the substrate; for caspase 6, Ac-Val-Glu-Ile-Asp-AMC was used as the substrate; for caspase 7, Ac-Asp-Glu-Val-Asp-AMC was used as the substrate; for caspase 8, Ac-Ile-Glu-Thr-Asp-AMC was used as the substrate; for caspase 9, Ac-Leu-Glu-His-Asp-AMC was used as the substrate; for caspase 10, Ac-Ile-Glu-Thr-Asp-AMC was used as the substrate (Nicholson, D.W. and Thornberry, N.A., *TIBS*, 22, 299-306, 1997; Stennicke, H.R. and Salvesen, G.S., *J. Biol. Chem.*, 272(41), 25719-25723, 1997; Talanian, R.V., *et. al.*, *J. Biol. Chem.*, 272(15), 9677-9682, 1997; Wolf, B.B. and Green, D.R., *J. Biol. Chem.*, 274(29), 20049-20052, 1999). The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

15 Measurement of the apparent macroscopic binding (Michaelis) constants (K_M^{app}) for substrates

The apparent macroscopic binding constant (K_M^{app}) for each substrate was calculated, from the dependence of enzyme activity as a function of substrate concentration. The observed rates were plotted on the ordinate against the related substrate 20 concentration on the abscissa and the data fitted by direct regression analysis (Prism v 3.02; GraphPad, San Diego, USA) using Equation 1 (Cornish-Bowden, A. *Fundamentals of enzyme kinetics* Portland Press; 1995, 93-128.).

$$v_i = \frac{V_{max}^{app} \cdot [S_o]}{[S_o] + K_M^{app}} \quad (1)$$

25

In Equation 1 'v_i' is the observed initial rate, 'V_{max}^{app}' is the observed maximum activity at saturating substrate concentration, 'K_M^{app}' is the apparent macroscopic binding (Michaelis) constant for the substrate, '[S_o]' is the initial substrate concentration.

Measurement of the inhibition constants

5 The apparent inhibition constant (K_i) for each compound was determined on the basis that inhibition was reversible and occurred by a pure-competitive mechanism. The K_i values were calculated, from the dependence of enzyme activity as a function of inhibitor concentration, by direct regression analysis (Prism v 3.02) using Equation 2 (Cornish-Bowden, A., 1995.).

10

$$v_i = \frac{V_{\max}^{\text{app}} \cdot [S]}{[S] + \{K_M^{\text{app}} \cdot ([I]/K_i)\}} \quad (2)$$

In Equation 2 ' v_i ' is the observed residual activity, ' V_{\max}^{app} ', is the observed maximum activity (i.e. in the absence of inhibitor), ' K_M^{app} ', is the apparent macroscopic binding (Michaelis) constant for the substrate, '[S]' is the initial substrate concentration, ' K_i ' is the apparent dissociation constant and '[I]' is the inhibitor concentration.

15 In situations where the apparent dissociation constant (K_i^{app}) approached the enzyme concentrations, the K_i^{app} values were calculated using a quadratic solution in the form described by Equation 3 (Morrison, J.F. *Trends Biochem. Sci.*, 7, 102-105, 1982; Morrison, J.F. *Biochim. Biophys. Acta*, 185, 269-286, 1969; Stone, S.R. and Hofsteenge, J. *Biochemistry*, 25, 4622-4628, 1986).

$$v_i = \frac{F\{E_o - I_o - K_i^{\text{app}} + \sqrt{(E_o - I_o - K_i^{\text{app}})^2 + 4 \cdot K_i^{\text{app}} \cdot E_o}\}}{2} \quad (3)$$

25

$$K_i^{\text{app}} = K_i(1 + [S_o]/K_M^{\text{app}}) \quad (4)$$

In Equation 3 ' v_i ' is the observed residual activity, 'F' is the difference between the maximum activity (i.e. in the absence of inhibitor) and minimum enzyme activity, ' E_o ' is the total enzyme concentration, ' K_i^{app} ' is the apparent dissociation constant and ' I_o ' is the inhibitor concentration. Curves were fitted by non-linear regression

analysis (Prism) using a fixed value for the enzyme concentration. Equation 4 was used to account for the substrate kinetics, where ' K_i ' is the inhibition constant, ' $[S_0]$ ' is the initial substrate concentration and ' K_M^{app} ' is the apparent macroscopic binding (Michaelis) constant for the substrate (Morrison, 1982).

5

The second-order rate of reaction of inhibitor with enzyme

Where applicable, the concentration dependence of the observed rate of reaction (k_{obs}) of each compound with enzyme was analysed by determining the rate of 10 enzyme inactivation under pseudo-first order conditions in the presence of substrate (Morrison, J.F., *TIBS*, 102-105, 1982; Tian, W.X. and Tsou, C.L., *Biochemistry*, 21, 1028-1032, 1982; Morrison, J.F. and Walsh, C.T., from Meister (Ed.), *Advances in Enzymol.*, 61, 201-301, 1988; Tsou, C.L., from Meister (Ed.), *Advances in Enzymol.*, 61, 381-436, 1988;). Assays were carried out by addition of various concentrations 15 of inhibitor to assay buffer containing substrate. Assays were initiated by the addition of enzyme to the reaction mixture and the change in fluorescence monitored over time. During the course of the assay less than 10% of the substrate was consumed.

20

$$F = v_o t + \frac{(v_o - v_s) [1 - e^{(k_{obs} \cdot t)}]}{k_{obs}} + D \quad (5)$$

25

The activity fluorescence progress curves were fitted by non-linear regression analysis (Prism) using Eq. 5 (Morrison, 1969; Morrison, 1982); where 'F' is the fluorescence response, 't' is time, ' v_o ' is the initial velocity, ' v_s ' is the equilibrium steady-state velocity, ' k_{obs} ' is the observed pseudo first-order rate constant and 'D' is the intercept at time zero (*i.e.* the ordinate displacement of the curve). The second order rate constant was obtained from the slope of the line of a plot of k_{obs} versus the inhibitor concentration (*i.e.* $k_{obs}/[I]$). To correct for substrate kinetics, Eq. 6 was used, where ' $[S_0]$ ' is the initial substrate concentration and ' K_M^{app} ' is the apparent 30 macroscopic binding (Michaelis) constant for the substrate.

$$k_{inact} = \frac{k_{obs} (1 + [S_o]/K_M^{app})}{[I]} \quad (6)$$

Compounds of the invention were tested by the above described assays and observed
 5 to exhibit cruzipain inhibitory activity or inhibitory activity against an alternative CA
 C1 cysteine protease with an *in vitro* Ki inhibitory constant of less than or equal to
 100 μ M. Exemplary inhibition data for a number of example compounds of the
 invention are given in table 2.

Table 2. Exemplary inhibition data (Ki expressed as μ M).

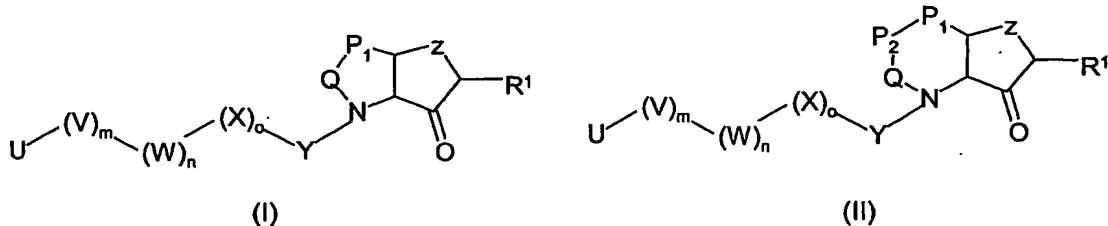
10

EXAMPLE N°	Cruzipain	Bovine Cathepsin S	Human Cathepsin L	Human Cathepsin K
3	0.2	>100	>35	>5
10	>5	>10	>25	0.1
48	>25	0.3	>100	>10
69	>5	>10	0.8	>100

15

CLAIMS

1. A compound according to general formula (I) or general formula (II): -



wherein: R^1 = C_{0-7} -alkyl (when $C = 0$, R^1 is simply hydrogen), C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl (when $C = 0$, R^1 is simply an aromatic moiety Ar);

10 Z = O, S, CR²R³ or NR⁴, where R⁴ is chosen from C₀₋₇-alkyl, C₃₋₆-cycloalkyl or Ar-C₀₋₇-alkyl;

$$P^1 = CR^5R^6,$$

$$15 \quad P^2 = CR^7R^8,$$

$Q = CR^9R^{10}$ or NR^{11} , where R^{11} is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl;

20 Each of R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} is independently chosen from $C_{0.7}$ -alkyl, $C_{3.6}$ -cycloalkyl, $Ar-C_{0.7}$ -alkyl, $O-C_{0.7}$ -alkyl, $O-C_{3.6}$ -cycloalkyl, $O-Ar-C_{0.7}$ -alkyl, $S-C_{0.7}$ -alkyl, $S-C_{3.6}$ -cycloalkyl, $S-Ar-C_{0.7}$ -alkyl, $NH-C_{0.7}$ -alkyl, $NH-C_{3.6}$ -cycloalkyl, $NH-Ar-C_{0.7}$ -alkyl, $N(C_{0.7}$ -alkyl) $_2$, $N(C_{3.6}$ -cycloalkyl) $_2$ or $N(Ar-C_{0.7}$ -alkyl) $_2$;

25

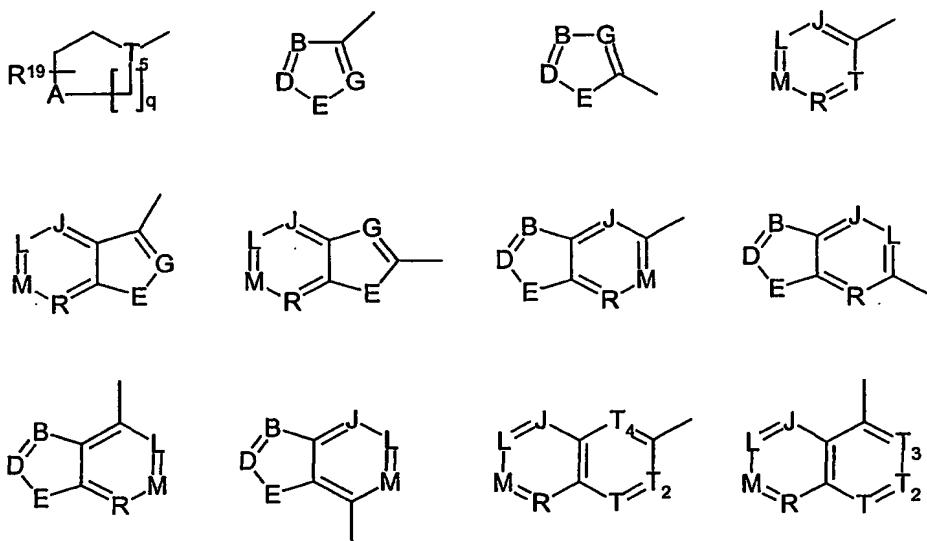
Y = CR¹²R¹³-CO, where R¹², R¹³ are chosen from C₀₋₇-alkyl, C₃₋₆-cycloalkyl or Ar-C₀₋₇-alkyl;

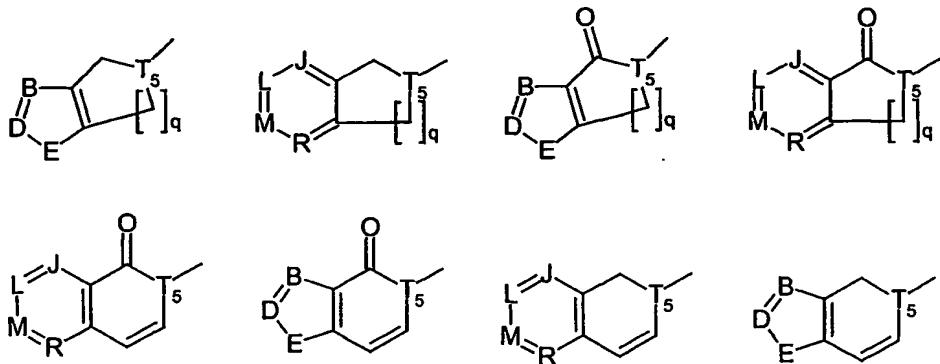
$(X)_o = CR^{14}R^{15}$, where R^{14} and R^{15} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and $Ar-C_{0-7}$ -alkyl and o is a number from zero to three;

5 $(W)_n = O, S, C(O), S(O)$ or $S(O)_2$ or NR^{16} , where R^{16} is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and $Ar-C_{0-7}$ -alkyl and n is zero or one;

10 $(V)_m = C(O), C(S), S(O), S(O)_2, S(O)_2NH, OC(O), NHC(O), NHS(O),$
 $NHS(O)_2, OC(O)NH, C(O)NH$ or $CR^{17}R^{18}$, where R^{17} and R^{18} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl and m is a number from zero to three, provided that when m is greater than one, $(V)_m$ contains a maximum of one carbonyl or sulphonyl group;

15 $U =$ a stable 5- to 7-membered monocyclic or a stable 8- to 11-membered bicyclic ring which is either saturated or unsaturated and which includes zero to four heteroatoms (as detailed below):





wherein R^{19} is:

5

C_{0-7} -alkyl, C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl, $O-C_{0-7}$ -alkyl, $O-C_{3-6}$ -cycloalkyl, $O-Ar-C_{0-7}$ -alkyl, $S-C_{0-7}$ -alkyl, $S-C_{3-6}$ -cycloalkyl, $S-Ar-C_{0-7}$ -alkyl, $NH-C_{0-7}$ -alkyl, $NH-C_{3-6}$ -cycloalkyl, $NH-Ar-C_{0-7}$ -alkyl, $N(C_{0-7}$ -alkyl) $_2$, $N(C_{3-6}$ -cycloalkyl) $_2$ or $N(Ar-C_{0-7}$ -alkyl) $_2$; or, when part of a CHR^{19} or CR^{19} group, R^{19} may be halogen;

A is chosen from:

CH_2, CHR^{19}, O, S and NR^{20} ;

10

where R^{19} is as defined above; and R^{20} is chosen from:

C_{0-7} -alkyl, C_{3-6} -cycloalkyl and $Ar-C_{0-7}$ -alkyl;

B, D and G are independently chosen from:

CR^{19} , where R^{19} is as defined above, or N;

15

E is chosen from:

CH_2, CHR^{19}, O, S and NR^{20} , where R^{19} and R^{20} are defined as above;

J, L, M, R, T, T_2 , T_3 and T_4 are independently chosen from:

20

CR^{19} and N, where R^{19} is as defined above;

T_5 is chosen from:

CH or N;

25

q is a number from one to three, thereby defining a 5-, 6- or 7-membered ring.

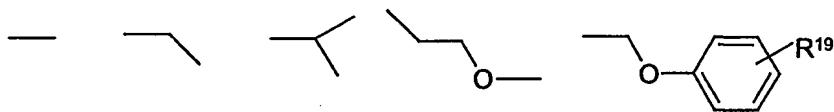
2. A compound as claimed in claim 1 wherein independently or in combination:

5 Z is O, S, CH₂, NH or NR⁴, where R⁴ is a Ar-C₁₋₄-alkyl or a substituted carbonyl or sulphonyl group;
P¹ and P² are CH₂; and
Q is CH₂ or NH.

10 3. A compound as claimed in claim 1 or claim 2 wherein R¹ comprises C₀₋₇-alkyl or Ar-C₀₋₇-alkyl.

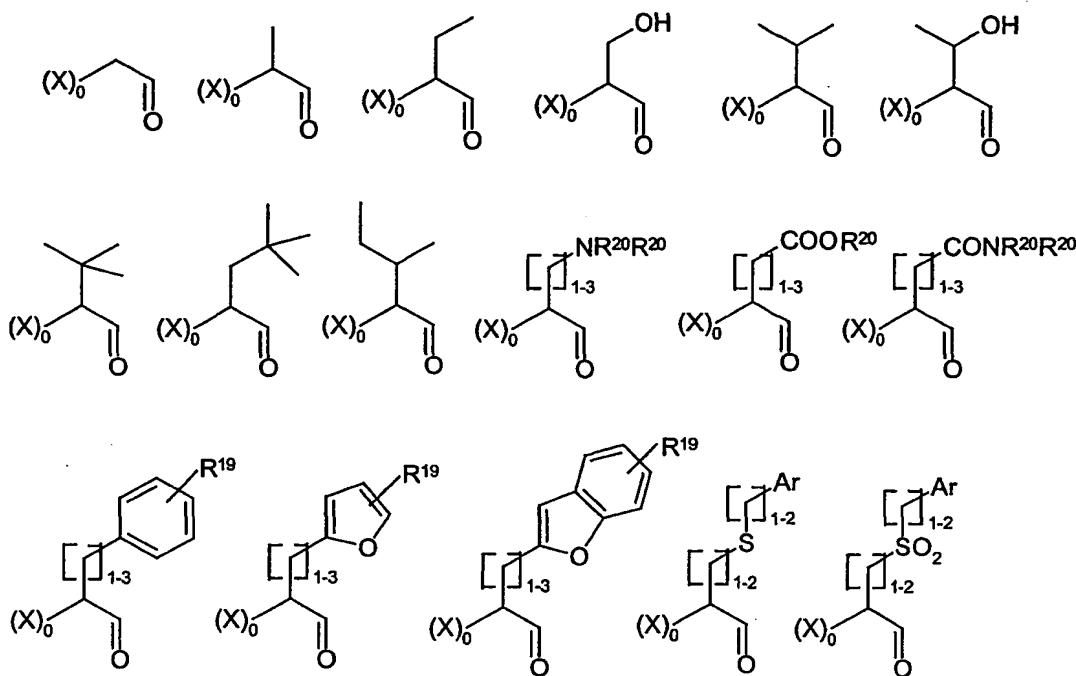
4. A compound as claimed in claim 3 wherein R¹ is selected from hydrogen or one of the following moieties:

15



5. A compound as claimed in any one of claims 1 to 4 wherein Y is CR¹²R¹³CO where R¹², R¹³ are selected from C₀₋₇-alkyl, C₃₋₆-cycloalkyl or Ar-C₀₋₇-alkyl.

20 6. A compound as claimed in claim 5 where Y is selected from one of the following moieties:



wherein R¹⁹, R²⁰ and Ar are as defined above.

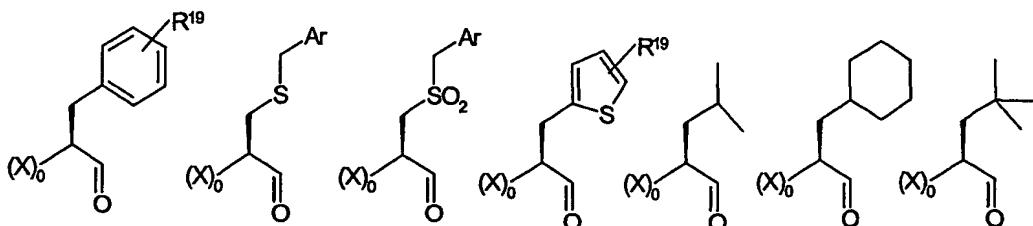
7. A compound as claimed in any one of claims 1 to 4 wherein Y is CHR¹³CO
5 where R¹³ is Ar-CH₂-, where the aromatic ring is an optionally substituted phenyl or monocyclic heterocycle.

8. A compound as claimed in any one of claims 1 to 4 wherein Y is CHR¹³CO
where R¹³ is a simple branched alkyl group or a straight heteroalkyl chain.

10

9. A compound as claimed in any one of claims 1 to 4 wherein Y is CHR¹³CO
where R¹³ comprises cyclohexylmethyl.

10. A compound as claimed in any one of claims 1 to 4 wherein Y is selected from
15 the following:

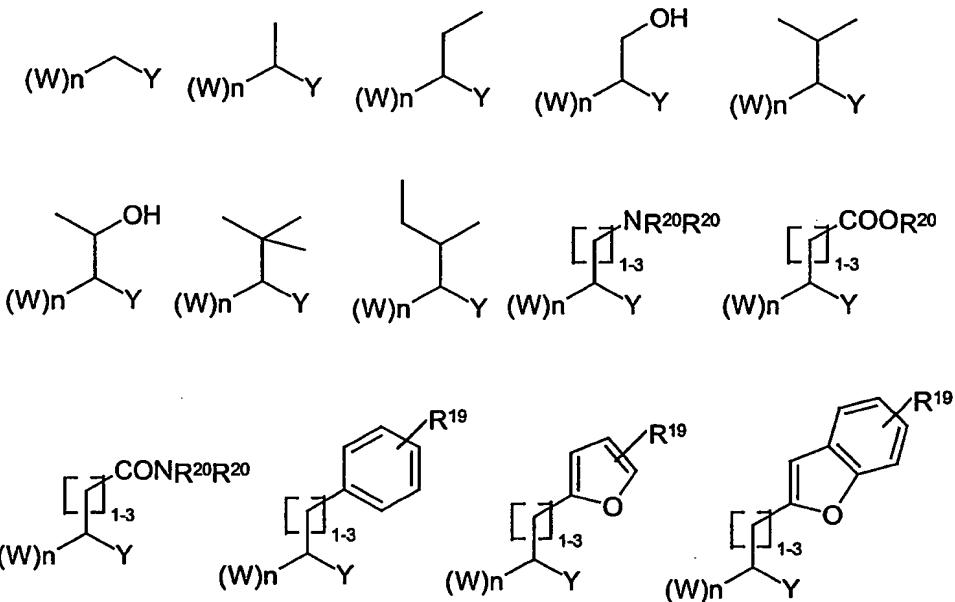


wherein R^{19} and Ar are as defined previously

11. A compound as claimed in any one of claims 1 to 10 wherein, in the group $(X)_o$, X is $CR^{14}R^{15}$ and each of R^{14} and R^{15} is selected from C_{0-7} -alkyl or $Ar-C_{0-7}$ -alkyl

5

12. A compound as claimed in any one of claims 1 to 11, wherein $(X)_o$ is one of the following moieties:



10

wherein R^{19} and R^{20} are as defined previously.

13. A compound as claimed in any one of claims 1 to 11, wherein $(X)_o$ a simple alkyl group and where $o = 0$ or 1 .

15

14. A compound as claimed in any one of claims 1 to 13 wherein, in the group $(W)_n$:

W is O , S , SO_2 , SO , $C(O)$ or NR^{16} , where R^{16} is C_{0-4} -alkyl; and n is 0 or 1 .

20

15. A compound as claimed in any one of claims 1 to 13 wherein, in the group $(W)_n$:

W is O , S , SO_2 , $C(O)$ or NH where n is 0 or 1.

5 16. A compound as claimed in any one of claims 1 to 13 wherein, in the group $(W)_n$:

NH where n is 1.

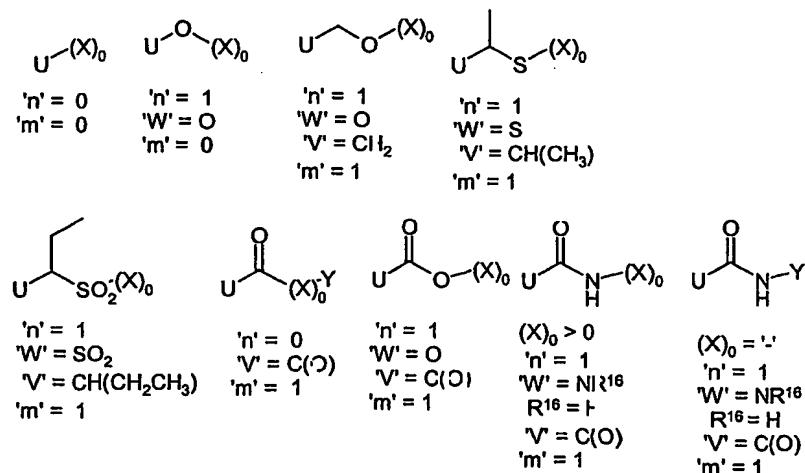
17. A compound as claimed in any one of claims 1 to 16 wherein, in the group

10 $(V)_m$:

V is $C(O)$, $C(O)NH$ or CHR^{18} , where R^{18} is C_{0-4} -alkyl; and
 m is 0 or 1.

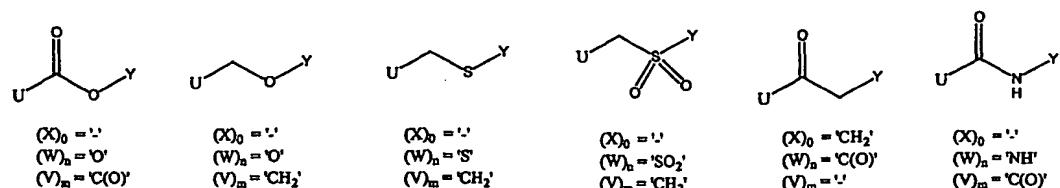
18. A compound as claimed in any one of claims 1 to 17 wherein the combination

15 $(V)_m$ and $(W)_m$ is one of the following:



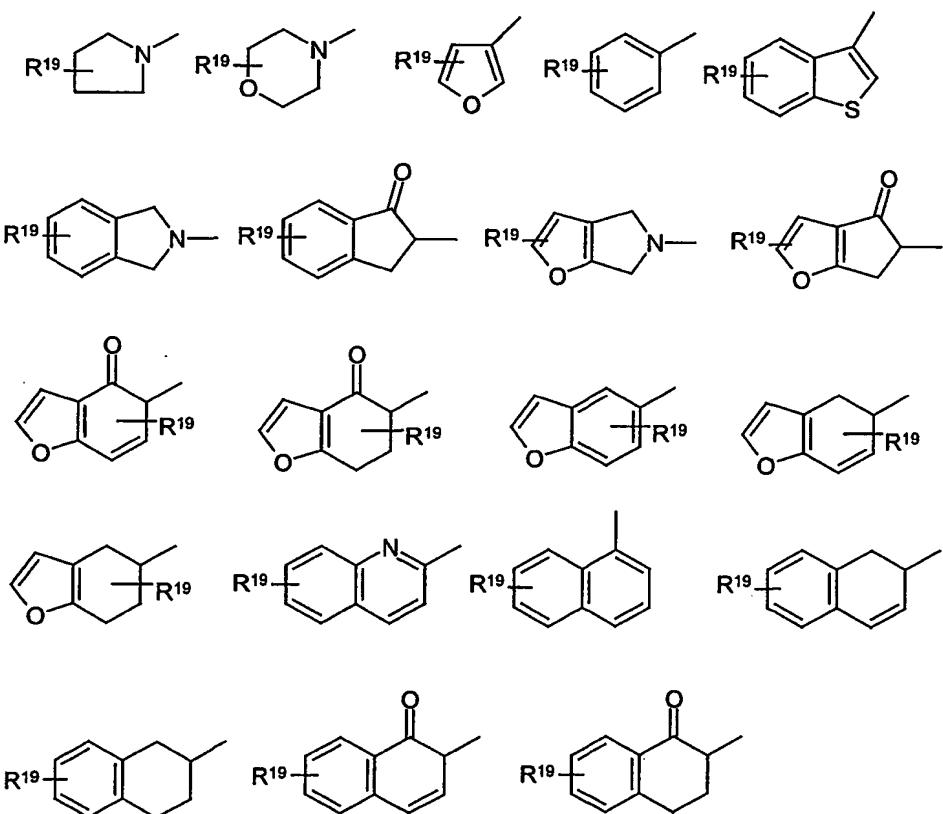
19. A compound as claimed in any one of claims 1 to 17 wherein the combination

$(X)_0$, $(V)_m$ and $(W)_m$ is one of the following:



20. A compound as claimed in any one of claims 1 to 19 wherein U comprises an optionally substituted 5- or 6-membered saturated or unsaturated heterocycle or an optionally substituted saturated or unsaturated 9- or 10-membered heterocycle.

5 21. A compound as claimed in claim 20 wherein U comprises one of the following:



wherein R^{19} is as defined previously.

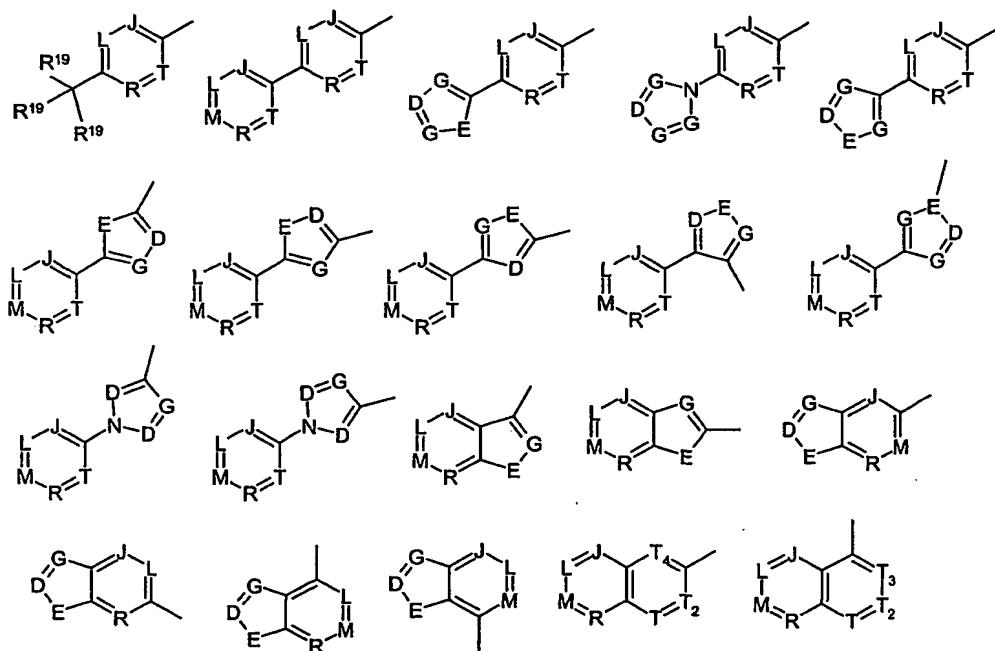
10

22. A compound as claimed in any one of claims 1 to 19 wherein U comprises a bulky alkyl or aryl group at the para position of an aryl Ar.

23. A compound as claimed in any one of claims 1 to 19 wherein U comprises a
15 meta or para-biaryl Ar-Ar, where Ar is as previously defined.

24. A compound as claimed in any one of claims 1 to 19 wherein U comprises a 6,6 or 6,5 or 5,6-fused aromatic ring.

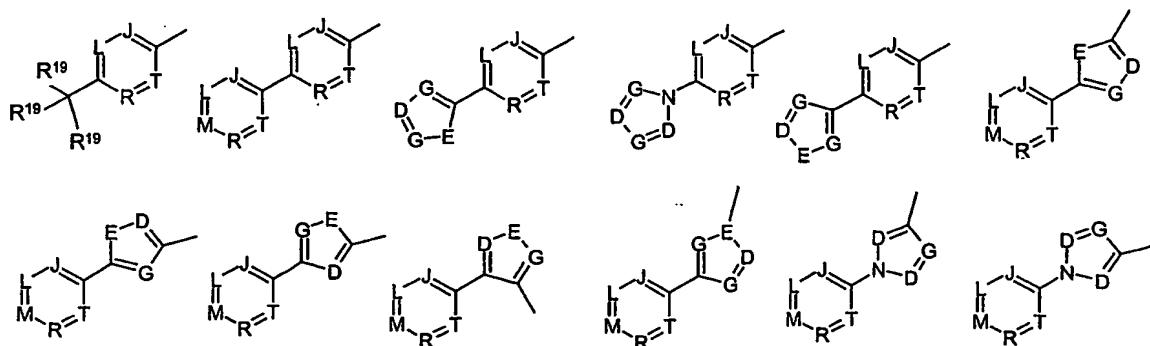
25. A compound as claimed in any one of claims 1 to 19, wherein U represents a 5 group:



wherein R^{19} , D, E, G, J, L, M, R, T, T_2 , T_3 and T_4 are as defined previously.

10

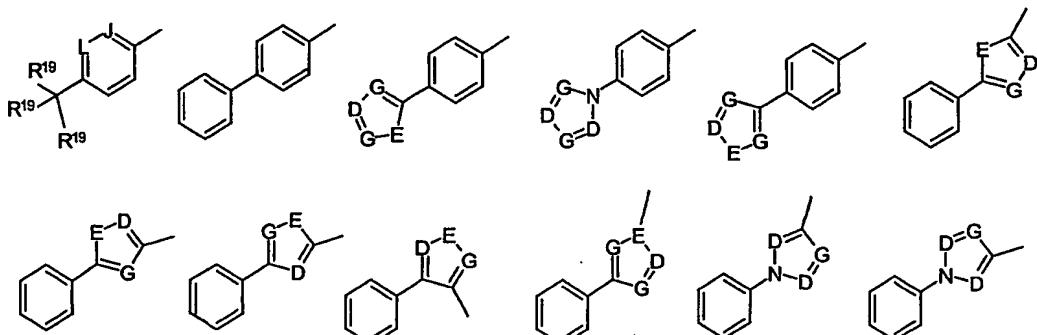
26. A compound as claimed in any one of claims 1 to 19, wherein U represents a group



wherein R^{19} , D, E, G, J, L, M, R and T are as defined previously.

27. A compound as claimed in any one of claims 1 to 19, wherein U represents a group

5



wherein R^{19} , D, E, G, J and L are as defined previously.

28. A method of validating a known or putative cysteine protease inhibitor as a therapeutic target, the method comprising:

10

(a) assessing the *in vitro* binding of a compound as claimed in any one of claims 1 to 27 to an isolated known or putative cysteine protease, providing a measure of 'potency'; and optionally, one or more of the steps of:

15

(b) assessing the binding of a compound as claimed in any one of claims 1 to 27 to closely related homologous proteases of the target and general house-keeping proteases (e.g. trypsin) to provides a measure of 'selectivity';

20

(c) monitoring a cell-based functional marker of a particular cysteine protease activity, in the presence of a compound as claimed in any one of claims 1 to 27; and

(d) monitoring an animal model-based functional marker of a particular cysteine protease activity, in the presence of a compound as claimed in any one of claims 1 to 27.

25

29. The use of a compound as claimed in any one of claims 1 to 27 in the validation of a known or putative cysteine protease inhibitor as a therapeutic target.
30. A compound as claimed in any one of claims 1 to 27 for use in medicine,
5 especially for preventing or treating diseases in which the disease pathology may be modified by inhibiting a cysteine protease.
31. The use of a compound as claimed in any one of claims 1 to 27 in the preparation of a medicament for preventing or treating diseases in which the disease
10 pathology may be modified by inhibiting a cysteine protease.
32. A compound as claimed in any one of claims 1 to 27 for use in preventing or treating Chagas' disease.
- 15 33. A compound as claimed in any one of claims 22 to 27 for use in preventing or treating Chagas' disease.
34. The use of a compound as claimed in any one of claims 1 to 27 in the preparation of a medicament for preventing or treating Chagas' disease.
- 20 35. The use of a compound as claimed in any one of claims 22 to 27 in the preparation of a medicament for preventing or treating Chagas' disease.
36. A pharmaceutical or veterinary composition comprising one or more
25 compounds as claimed in any one of claims 1 to 27 and a pharmaceutically or
veterinarily acceptable carrier.
37. A process for the preparation of a pharmaceutical or veterinary composition as
claimed in claim 36, the process comprising bringing the active compound(s) into
30 association with the carrier, for example by admixture.